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PHOSPHATE CLEARANCE AND TUBULAR REABSORPTION OF PHOSPHATE IN PATIENTS WITH PARATHYROID DISORDERS AND RENAL FAILURE

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Parathyroid disorders may often be difficult to recognize clinically, particularly hyperparathyroidism, where the concentration of serum calcium and serum phosphate need not necessarily be increased or reduced, respectively, especially when complicated by renal calculus, nephrocalcinosis or renal failure (2, 29, 34, and others). However, according to various authors (1, 2, 13, 27, 29, and others) the parathyroid hormone has an inhibiting effect on the phosphate reabsorption in the renal tubules. Efforts have been made to utilize this fact in the diagnosis of parathyroid disorders by determining the "phosphate clearance" (14, 21, and others). Kyle et al. (21) report that this parameter is of particular value when determination of the serum calcium and serum phosphate does not yield any information. The normal phosphate clearance is said to be from 6.3 to 15.5 ml per minute and the value is increased in hyperparathyroidism and reduced in hypoparathyroidism. Renal failure is stated to cause reduced values when the glomerular filtration falls to below 25 ml per minute. Increased values are found in osteomalacia as a result of the accompanying secondary hyperparathyroidism, whilst normal values are found in osteoporosis. Kyle et al. (21) report also that there are variations during the 24 hours of the day, the clearance being somewhat higher in the afternoon than in the morning.

Other workers have tried to use the tubular reabsorption as percentage of the amount of glomerular filtered phosphate in the form of a function test (TRP %) (5, 7, 8, 12, 29, 30, 31, 33, 35, 37, 38, 39, and others). The technique of the test is that the glomerular filtration is evaluated by means of the creatinine clearance. By subtracting from 100 the phosphate clearance as percentage of the creatinine clearance, the tubular reabsorption of phosphate as percentage of the amount of glomerular filtration is obtained.

$$\text{TRP \%} = (1 - \frac{\text{phosphate clearance}}{\text{creatinine clearance}}) \times 100$$

If the values for phosphate and creatinine clearance are inserted into the formula:

$$(\text{Phosphate clearance} = \frac{\text{diuresis} \times \text{urine phosphate}}{\text{serum phosphate} \times \text{time}} \text{ and}$$

$$\text{creatinine clearance} = \frac{\text{diuresis} \times \text{urine creatinine}}{\text{serum creatinine} \times \text{time}})$$

then

$$\text{TRP\%} = (1 - \frac{\text{urine phosphate} \times \text{serum creatinine}}{\text{serum phosphate} \times \text{urine creatinine}}) \times 100\%$$

The advantage of this method is that diuresis is not included. Use of these formulas assumes both that creatinine clearance equals the amount of the glomerular filtration, and also that all non-organic phosphate is diffusible through the glomerular membrane. Several authors consider that this is so (16, 38), but Fuchs et al. (6) and Walser (40) have shown that about 10 per cent of the organic phosphate in serum is not readily diffusible. So the calculated TRP % is only an approximation.

The normal value for tubular phosphate reabsorption is said to be about from 80 to 95 per cent of the amount of filtered phosphate. The values are decreased in hyperparathyroidism and osteomalacia and increased in hypoparathyroidism. The reason for the low values in osteomalacia is reported to be the accompanying secondary hyperparathyroidism (5, 8, 29, 31, 36). It has also been stated that the TRP % may be reduced in bone metastases and multiple myeloma (8, 29, 31, 37).

There is not complete agreement regarding the clinical value of these laboratory tests. Some workers have reported that the TRP % may be normal in hyperparathyroidism (19, 24, 32) and

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it will be seen from the foregoing that in various different conditions without primary hyperparathyroidism reduced TRP % and increased phosphate clearance may be seen. The content of phosphate in the diet seems to be of significance. If the diet is lacking in phosphate the phosphate clearance falls and the TRP % increases. This may be the reason why normal TRP % has been found in parathyroid adenoma (31). However, if the diet contains much phosphate, the phosphate clearance will increase and the TRP % fall, though only to a slight extent in normal persons (5, 7, 9, 31).

In order to make these parameters more specific in the diagnosis of parathyroid adenoma, the TRP % has been combined with intravenous calcium infusion (3, 5, 8, 10, 15, 17, 22, 30, 37). Generally 10-15 mg calcium per kilogram of body weight has been administered in the course of a few hours. There is agreement that the excretion of phosphate in the urine falls and that the TRP % becomes increased in normal persons. The reason is thought to be that calcium infusion increases the plasma calcium and thereby inhibits the parathyroid function. The same can be seen in bone metastases and osteomalacia (22, 30). However, in parathyroid adenoma no increase in TRP % is found (17, 22, 30, 37) though Chambers et al. (5) report that some patients with that condition may react in the same way as normal persons.

The aim of the present study was to try out the technique mentioned above, and to evaluate its practicability in clinic, particularly in patients with varying degrees of renal failure, a complication often encountered in parathyroid adenoma.

TECHNIQUE

In order to avoid too great variations in the intake of phosphate, the patients were given special diet on the day of the examination, *i. e.*, minus milk, cheese and sugar. The first-named two foods were avoided because of their content of phosphate, and sugar because of a considerable rise in blood sugar is thought to cause increased phosphate clearance (18).

The patients were given about half to one litre fluid per hour but tap water was avoided. Urine was collected in the periods 9 a. m. to 1 p. m. and 1 p. m. to 5 p. m. and urine phosphate and urine creatinine determinations carried out. In the middle of each experimental period a blood test was taken for determination of serum phosphate *a. m.* Müller (28) and serum creatinine *a. m.* Bonsnes & Taussky (4). Phosphate and creatinine clearance and TRP % were calculated for each 4-hourly period according to the formulas mentioned above.

Where calcium infusion was performed, this was done during another experimental period, 15 mg calcium per kilogram of body weight (1 ml 10 per cent calcium gluconate = 10 mg Ca) being administered. The calculated amount of calcium was mixed in 500 ml 0.9 per cent sodium chloride solution and infused intravenously between 9 a. m. and 1 p. m. During this and the following 4-hourly period phosphate clearance and TRP % were measured.

Determination of calcium excretion in urine with normal diet was also determined according to the EDTA method (23). Where the diurnal excretion was greater than 300 mg the determinations were repeated after three days' diet containing little calcium (< 150 mg per day). As a result the diurnal excretion generally falls to below 150 mg (10).

Finally the serum calcium concentration (EDTA method) and the alkaline phosphatase (Kind & King, 20) were measured.

RESULTS

1. *Normal persons.*

Phosphate clearance and TRP % determination were carried out on 14 persons with no endocrinic disturbances, bone affections, dyspeptic symptoms or kidney disease. Calcium excretion was normal in all cases, as was also serum phosphate, serum calcium and creatinine clearance.

With the technique used, the phosphate clearance varied between 6.8 and 14.8 ml per minute and the TRP between 83.8 per cent and 92.3 per cent. The mean average of the two daily determinations was used. Age and sex did not seem to have any influence in this study. The normal values were about the same as those found by other investigators.

The daily variations in serum phosphate, phosphate and creatinine clearance and TRP % were analysed and the results from the 9 a. m. to 1 p. m. and 1 p. m. to 5 p. m. periods compared. The serum phosphate and creatinine clearance did not alter significantly (m = + 0.04 mmol per litre and m = — 3.1 ml per minute; s = ± 0.19 mmol per litre and s = ± 3.6 ml per minute), but the phosphate clearance rose in all cases except one (m = 3.6 ml per minute; s = ± 1.98 ml per minute), while the TRP % fell in all patients (m = — 5.8 per cent; s = ± 2.7 per cent). This is in agreement with the experience of Kyle et al. (21).

Calcium infusion was carried out in three cases, with the result that the TRP % rose from 84.4 per cent, 92.3 per cent and 89.4 per cent to 89.0 per cent, 94.6 per cent and 91.2 per cent respectively in the period following calcium infusion — that is to day, there was a tendency to slight increase.

The influence of the parathyroid hormone on phosphate clearance and TRP % was examined on three normal persons. Two ml parathyroid extract (Meco-Dumex 2 ml = 20 Collip units = 5 U. S. P. units) was injected intramuscularly

daily for three days. The parameters were determined before the injections and on the third and sixth days after the first injection. The results are shown in Figs. 1 a and 1 b, from which it will be seen that the phosphate clearance rose (m = + 11.5 ml per minute) and the TRP % fell (m = —9.6 %). The serum phosphate was practically unchanged in two patients but fell in one patient. The serum calcium did not change to any degree and the creatinine clearance showed no definite alteration.

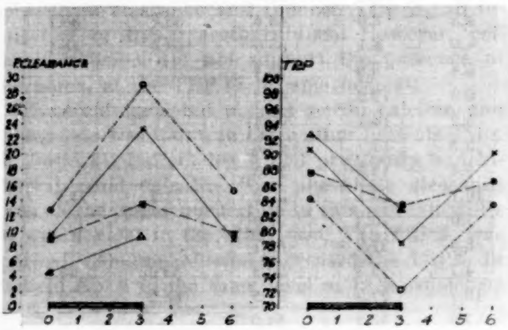


Fig. 1.

Effect of 20 Collip Units Parathyroid Hormone Daily for 3 Days on Phosphate Clearance (a) and Tubular Reabsorption of Phosphate (b).

Abscissa: Days.
Ordinate: Phosphate clearance in ml per minute (a). Tubular reabsorption of phosphate as percentage of filtered amount (b).

×———× }
■– – – –■ } Normal
○—·—·—○ }
△———△ Hypoparathyroidism.

2. *Parathyroid disorders.*

Only few patients in this group were examined, *viz.,* one with parathyroid adenoma verified surgically and two with hypoparathyroidism following strumectomy. A further five patients were included who had hypercalciuria and suspicion of parathyroid adenoma but where this diagnosis could not be confirmed on follow-up studies.

A. *Parathyroid adenoma:* In 1956 a parathyroid adenoma was removed from a 48-year old man who at that time had bone changes of the osteitis fibrosa type, high serum calcium, low serum phosphate, increased alkaline phosphatases and hypercalciuria. Follow-up was made in 1958. The bone condition was unchanged but the concentrations of phosphate and calcium in the serum were normal, as was the excretion of calcium in the urine. However, the phosphate clearance was elevated and the TRP % reduced. The creatinine clearance was normal but the kidney concentration power was found to be reduced. Calcium was infused, which resulted in the TRP % rising to about the same level as in normal persons (No. 1 a, Table 1). The patient was re-examined a year later. There was then hypercalciuria and reduced serum phosphate and again increased phosphate clearance and reduced TRP %. Calcium infusion caused the TRP % to fall, thus indicating parathyroid adenoma (No. 1 b, Table 1). An exploratory operation confirmed this and the adenoma was removed*). On follow-up four months later (No. 1 c, Table 1) the serum phosphate and phosphate clearance were normal but

*) Parathyroidadectomy was performed at Surgical Department D, The University Hospital (Rigshospital), Copenhagen.

Table 1.

Phosphate Clearance and Percentage Tubular Reabsorption of Phosphate in a Patient with Parathyroid Adenoma (No. 1), Two Patients with Hypoparathyroidism (Nos. 2—3) and Five Patients with Hypercalciuria (Nos. 4—8).

No.	Sex	Age	Serum calcium (4.5—5.5 meq/l)	**Serum phosphate (0.9—1.5 mmol/l)	Alk. phosphatase (< 10 units /100 ml)	*Urine calcium (150—300 mg/day)	**Phosphate clearance (6.0—15.0 ml/min.)	**Creatine clearance (>67 ml/min.)	**TRP per cent (83—93 per cent)	TRP per cent during Ca infusion	TRP per cent after Ca infusion
1a	M	51	4.9	0.97	10.6	197	19.6	72.1	71.7	83.7	78.4
1b		52	5.1	0.88	12.9	455→364	19.1	66.6	70.2	73.1	58.9
1c		52	4.9	1.29		330—315	14.4	62.2	76.9	89.1	89.6
2	W	66	4.1	1.41	5.8	37	4.4	60.0	92.8	93.0	81.9
3	W	51	4.2	1.23	15.3		4.9	70.2	93.1		
4	M	50	7.1→4.4	0.65	11.9	450—151	21.6	75.8	72.3	66.8	80.8
5	M	54	4.7	0.76	6.3	472—252	18.4	81.0	77.6	77.2	85.0
6	M	50	4.8	1.19	5.4	442—282	15.6	108.7	85.8	87.4	90.5
7	M	59	4.9	1.14	4.7	321—260	13.7	87.3	83.7		
8	W	61	5.0	1.21	10.0	681—324	5.9	71.9	92.1		

*) The first of two figures in column "Urine calcium" means excretion after ordinary food and second the excretion after calcium restricted food.

**) Figures are the means of two daily determinations.

Table 2.

Phosphate Clearance and Percentage Tubular Reabsorption of Phosphate in 29 Patients with Kidney Insufficiency.

No.	Sex	Age	Calculus	Serum calcium (4.5—5.5 meq/l)	*Serum phosphate (0.9—1.5 mmol/l)	*Phosphate clearance (6.0—15.0 ml/min.)	*Creatine clearance (>67 ml/min.)	*TRP per cent	TRP per cent during Ca infusion	TRP per cent after Ca infusion
1	W	46	÷	2.6	5.45	0.7	1.2	39.9		
2	W	38	÷	4.8	1.82	2.9	4.6	22.2		
3	W	58	÷	4.8	2.20	3.2	5.2	21.5	18.5	20.5
4	W	52	÷	5.0	1.29	3.5	5.8	28.2		
5	M	60	÷	4.2	1.74	3.8	5.9	36.7		
6	W	32	÷	4.0	1.78	4.8	7.8	46.5		
7	M	72	+	4.9	1.37	4.5	8.0	43.4	36.7	38.1
8	W	70	÷	4.0	1.52	4.9	8.1	39.0	43.6	48.4
9	M	42	÷	5.2	1.80	5.8	8.6	33.4		
10	W	64	÷	4.4	2.42	6.9	12.0	42.2		
11	W	55	++	4.6	0.93	6.2	14.1	65.4		
12	W	78	÷	4.3	1.01	5.3	17.7	67.3		
13	W	60	÷	3.6	0.94	9.4	19.5	52.3		
14	W	59	÷	5.4	1.48	10.1	20.1	57.9	71.1	74.9
15	W	65	÷	4.6	1.04	7.0	20.3	66.0		
16	W	65	÷	5.0	1.15	8.0	21.2	62.1		
17	W	83	+	4.9	1.20	4.7	23.4	80.3	83.0	86.1
18	W	26	++	4.1	0.73	15.7	27.0	37.2	68.2	72.5
19	W	40	÷	5.7	1.14	7.0	33.9	84.0		
20	W	75	÷	4.7	1.17	6.5	40.6	83.9		
21	W	67	÷	—	0.85	7.1	42.6	87.7		
22	W	58	+	4.5	1.46	4.3	42.7	90.2		
23	W	80	++	4.5	1.24	7.5	48.3	83.5		
24	W	77	+	—	1.01	10.6	49.8	78.6		
25	M	74	÷	4.8	0.93	8.9	53.3	83.6		
26	W	60	+	4.9	0.95	11.6	70.2	83.5		
27	W	32	+	5.0	1.02	11.1	72.8	88.1		
28	M	45	+	4.7	1.26	9.7	91.3	88.2		
29	M	55	+	4.8	1.30	12.9	91.6	85.9		

+) = Unilateral renal calculus.
++) = Bilateral renal calculus.
*) = Figures are the means of two daily determinations.

there was still hypercalciuria and the TRP % was slightly reduced. Calcium infusion caused the TRP % to rise to normal level. As anticipated from the experiences reported in the literature, increased phosphate clearance and reduced TRP % which could not be normalized by calcium infusion but which decreased even further (No. 1 b), were found in this patient with parathyroid adenoma.

B. *Hypoparathyroidism:* Two patients (Table 1, Nos. 2 and 3) showed signs of hypoparathyroidism following strumectomy. All were euthyroid. The Chvostek symptom was positive and the serum calcium reduced. There was reduced phosphate clearance and TRP % on the upper borderline in both cases. Calcium infusion performed on patient No. 2 resulted in a rise in phosphate clearance and a reduction in TRP %, as also reported by N o r d i n et al. (30) and others. The patient was treated with 20 Collip units parathyroid hormone daily for three days. As anticipated, the phosphate clearance rose while the TRP % fell (Fig. 1).

C. *Hypercalciuria:* Table 1 also shows five patients with hypercalciuria who were under observation for parathyroid adenoma but where the diagnosis could not be confirmed by subsequent examinations (Nos. 4—8). None of these patients had bone affections and all had normal creatinine clearance and kidney concentration power. Patient No. 4**) was suffering from stomach ulcer and pyloric stenosis and vomitting. Before admission he had drunk large quantities of milk and alkaline. There was slight alkalosis and the

**) This patient was admitted to Medical Department B, Frederiksberg Hospital. The writer is indebted to Dr. K. S c h m i t h, Chief Physician of that department, for his cooperation in allowing the tests to be carried out.

serum calcium was increased but fell gradually. The serum phosphate was low. In addition, there was hypercalciuria, increased phosphate clearance and reduced TRP %, all indicating hyperparathyroidism. However, calcium infusion almost normalized the TRP %, which would contraindicate parathyroid adenoma. The high phosphate clearance in this patient was probably due to his high intake of food containing phosphate (milk).

Patient No. 5 had previously had bilateral renal calculus and at the time of examination had low serum phosphate, hypercalciuria, increased phosphate clearance and reduced TRP %, all indicative of hyperparathyroidism. However, calcium infusion did not support the presence of adenoma, at the TRP % became normal.

Hypercalciuria but normal serum calcium and phosphate was found in three other patients (Nos. 6, 7 and 8). Patient No. 6 had previously had bilateral renal calculus. The phosphate clearance was on the upper borderline in this patient, while it was normal in the other two. The TRP% was normal. Calcium infusion increased the TRP% in patient No. 6 to the same level as in normal persons.

3. *Renal failure.*

A total of 29 patients with varying degrees of renal failure were examined. Table 2 gives some laboratory data regarding the patients, arranged according to the size of the creatinine clearance value. Four had normal creatinine clearance. (Nos. 26—29) but were examined on account of renal calculus. All the patients had chronic pyelonephritis, except No. 3 who had cysts of the kidney, No. 9 who had chronic glomerulonephritis and No. 29 who had nephrosclerosis.

There was reduced serum calcium in eight patients (Nos. 1, 5, 6, 8, 10, 12, 13, 18) and increased serum phosphate in eight (Nos. 1, 2, 3, 5, 6, 8, 9, 10), all of whom had creatinine clearance below 30 ml per minute. This is a well-known phenomenon in severe cases of renal failure. In one patient (No. 19) there was slightly increased serum calcium concentration and in one (No. 18) reduced serum phosphate. None had hypercalciuria. Bone disorders were not seen, except for halisteresis which was demonstrated in five patients (Nos. 8, 11, 13, 20 and 26). Three of these had increased alkaline phosphate in serum (Nos. 8, 13, 20). However, three others (Nos. 10, 14, 17) showed increase of the alkaline phosphatases without roentgenological bone changes.

Twelve of the patients had reduced phosphate clearance (Nos. 1—9, 12, 17, 22) and 19 reduced TRP % (Nos. 1—18, 24). The total serum protein concentration was normal, except in eight patients (Nos. 1, 3, 4, 8, 9, 12, 27 and 29) where it was slightly reduced.

The phosphate clearance and TRP % values can also be seen from Figs. 2 and 3 which include the

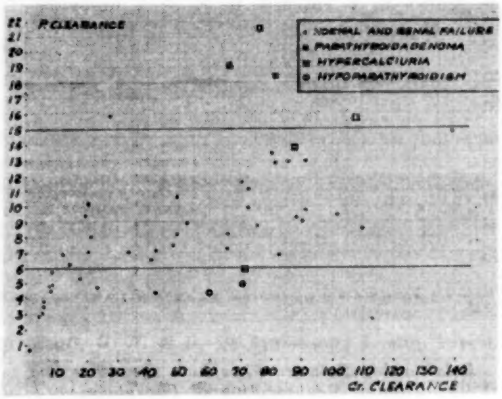


Fig. 2.

Relationship Between Phosphate Clearance and Creatinine Clearance.

Abscissa: Creatinine clearance in ml per minute.
Ordinate: Phosphate clearance in ml per minute.

patients shown in Table 1. Where the creatinine clearance fell to below 20 ml per minute there was a severe reduction in the phosphate clearance, probably due to the impaired glomerular function. Increased creatinine clearance was accompanied by slightly elevated phosphate clearance.

As far as TRP % is concerned, here again there was a sharp decrease when the creatinine clearance fell to below about 30 ml per minute. The reason for this is probably the occurrence of secondary hyperparathyroidism, as mentioned by several workers (11, 29, and others). On the other hand, the TRP % seems to be independent of the creatinine clearance when the latter is higher than 30 ml per minute.

Calcium infusion was carried out in the usual way on six patients (Nos. 3, 7, 8, 14, 17, 18), with the result that the TRP % rose in all cases except in the two with the severest degree of renal failure (Nos. 3 and 7).

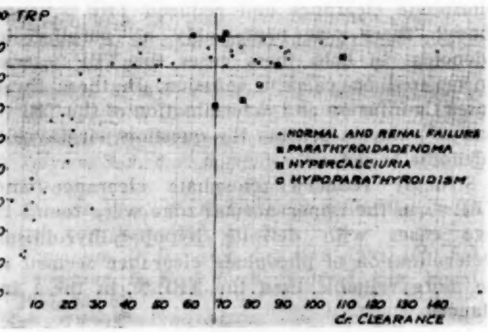


Fig. 3.

Relationship Between Tubular Reabsorption of Phosphate and Creatinine Clearance.

Abscissa: Creatinine clearance in ml per minute.
Ordinate: Tubular reabsorption of phosphate as percentage of filtered amount.

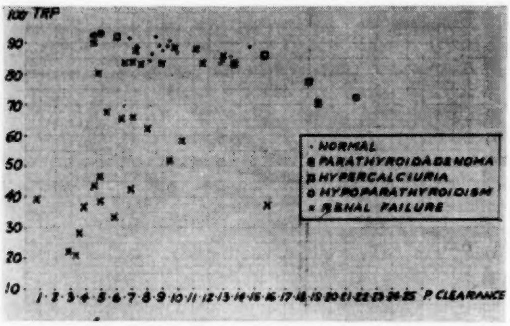


Fig. 4.
Relationship Between Phosphate Clearance and Tubular Reabsorption of Phosphate.

Abscissa: Phosphate clearance in ml per minute.
Ordinate: Tubular reabsorption of phosphate as percentage of filtered amount.

There was no difference between patients with renal calculus and those without, except for No. 18. That patient had low serum phosphate, high phosphate clearance and reduced TRP % in relation to the reduction in renal function, and therefore the suspicion of parathyroid adenoma arose. However, calcium infusion indicated the contrary, and it was not considered feasible to pursue that line of approach.

DISCUSSION

This material is too small to establish the value of phosphate clearance and TRP % in the diagnosis of hypoparathyroidism and hyperparathyroidism. Definitely increased phosphate clearance and reduced TRP % were found in the patient with parathyroid adenoma. The TRP % fell when calcium was infused. This would indicate the presence of adenoma, since otherwise, as mentioned, the TRP % would rise.

However, two patients with hypercalciuria and reduced serum phosphate also showed increased phosphate clearance and reduced TRP %, even though there was presumably no parathyroid adenoma. In both these cases the TRP % was normalized on calcium infusion. In these three cases Ca-infusion and determination of the TRP% was of value in settling the question parathyroid adenoma or not.

Strongly reduced phosphate clearance and TRP % in the upper normal zone were found in two cases with definite hypoparathyroidism. Determination of phosphate clearance seemed to be more valuable than the TRP % in these instances.

As far as the patients with renal failure were concerned (Fig. 2), a relationship between phosphate clearance and creatinine clearance was found also within the normal zone. In contrast, the TRP % seems to be independent of the creatinine clearance when the latter is higher than 30 ml per minute (Fig. 3). Calcium infusion caused the TRP % to rise definitely in only four out of six patients.

As a means of determining whether there is parathyroid adenoma, TRP % seems to be of more value than phosphate clearance if the creatinine clearance is more than 30 ml per minute, as the TRP % is then independent of it. In addition, TRP % determination has the advantage over phosphate clearance that measurement of diuresis need not be included. In cases where the creatinine clearance is lower than 30 ml per minute both parameters are difficult to evaluate. Here it is necessary to rely on calcium infusion in conjunction with the other clinical data, but, as mentioned, calcium infusion does not give reliable results in cases with severe renal failure.

Finally, the relation of serum phosphate to phosphate clearance and to TRP % was examined. No difinite relationship was found between serum phosphate and phosphate clearance, except that the patients with renal failure who had low phosphate clearance showed a tendency to increased serum phosphate. A similar relationship was found as regards serum phosphate and TRP %, in agreement with the observations of Reiss et al. (31). However, Milne (25), Milne et al. (26) and Nordin (29) found a connexion between falling TRP % and rising serum phosphate.

Fig. 4 shows the relationship between phosphate clearance and TRP %. As far as the normal persons were concerned, rising phosphate clearance was accompanied by falling TRP %, as was to be expected. However, other factors had an influence in the cases with renal failure, since reduced phosphate clearance was connected with reduced TRP %, probably because secondary hyperparathyroidism occurred and lowered the TRP %.

SUMMARY

Determinations of phosphate clearance and the tubular reabsorption of phosphate measured as percentage of the glomerular filtration (TRP %) was determined in 14 persons with no symptoms of dyspepsia, bone disorders, hormone disturbances or renal disease. The normal value for phosphate clearance was 6.0 to 15.0 ml per minute and for TRP % 83—93 per cent. In addition, one patient with verified parathyroid adenoma, two with definite hypoparathyroidism, five wth hypercalcuria and 29 patients with varying degrees of renal failure were examined, *i. e.* a total of 51 patients. Calcium infusion was carried out in 14 cases.

The patient with parathyroid adenoma showed high phosphate clearance and low TRP %. This finding was also observed in two of the patients with hypercalciuria. The two patients with hypoparathyroidism had low phosphate clearance and TRP % on the upper borderline. The patients with renal failure showed falling phosphate clea-

rance and TRP % when the creatinine clearance was below 20—30 ml per minute. Infusion of 15 mg calcium per kilogram of body weight caused the TRP % to rise in all the 14 patients examined, except in the patient with parathyroid adenoma, in the patient with hypoparathyroidism and in two of the patients with severe renal failure.

SUMMARIO

Thorkild Friis: CLEARANCE DE PHOSPHATO E REABSORPTION TUBULAR DE PHOSPHATO IN PATIENTES CON DISORDINES PARATHYROIDE E FALLIMENTO RENAL

Esseva executate determinationes del clearance de phosphato e del reabsorption tubular de phosphato in termino del percentage del filtration glomerular (RTP %) in 14 individuos sin ulle symptomas de dyspepsia, disordines ossee o hormonic, o morbo renal. Le valor normal del clearance de phosphato esseva 6.0—15.0 ml per minuta, e illo del RTP esseva 83—93 %. In plus esseva examinate un patiente con adenoma parathyroide verificate, duo con hypoparathyroidismo definite, cinque con hypercalciuria, e 29 patientes con fallimento renal de varie grados, i. e. un total de 51 patientes. Esseva institute infusion de calcium in 14 casos.

Le patiente con adenoma parathyroide monstrava alte clearance de phosphate e basse RTP %. Iste trovata esseva anque observate in duo del patientes con hypercalciuria. Le duo patientes con hypoparathyroidismo habeva un basse clearance de phosphato e un RTP % al limite superior. Le patientes con fallimento renal monstrava un diminution del clearance de phosphate e del RTP % quando le clearance de creatinina esseva minus que 20—30 ml per minuta. Infusion de 15 mg de calcium per kilogramma de peso de corpore faceva elevar se le RTP % in omne 14 patientes examinate salvo le patiente con adenoma parathyroide, ille con hypoparathyroidismo, e duo del patientes con sevor fallimento renal.

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PHOSPHATE CLEARANCE AND TUBULAR REABSORPTION OF PHOSPHATE IN PATIENTS WITH HYPERTHYROIDISM AND HYPOTHYROIDISM

By THORKILD FRIIS

A previous work reported the utilization of determination of phosphate clearance and the percentage tubular reabsorption of phosphate in parathyroid disorders and in patients with varying degrees of renal failure (14).

The genesis of the hypercalciuria often found in hyperthyroidism is not yet elucidated, and it is therefore considered of value to examine the phosphate clearance and tubular reabsorption of phosphate (TRP%) in a number of patients with thyroid disorders, in the hope of gaining information concerning the parathyroid function of such patients. If increased phosphate clearance and reduced TRP% were found, as is seen in hyperparathyroidism, this would tend to reduce the serum phosphate, which in turn would increase the serum calcium concentration and thus the urine calcium excretion.

Hypercalciuria in hyperthyroidism has been described by a number of authors (2, 11, 24, 27, 29, 36). In connection with that disorder, halisteresis if often found roentgenologically in up to half the reported cases with thyrotoxicosis (8, 15, 32). In addition, a few have also observed hypercalcaemia, though generally the serum phosphate is normal (11, 24, 27, 36, 39, 40).

Some workers consider that hypercalciuria and halisteresis are due to greater bone decomposition as the result of increased calcium turnover, probably caused by the direct influence of the thyroxin on the bone salts (2, 25). Others think that the halisteresis is due to defective formation of bone matrix as the result of relative vitamin deficiency and increased protein catabolism (17, 33). There are also those who are of the opinion that simultaneous hyperparathyroidism is responsible for the hypercalciuria and skeletal changes (18). This hypothesis is based on animal experiments (9, 10), on clinical observation of the simultaneous occurrence of hyperthyroidism and hyperparathyroidism (12, 19, 20), and on histological examination of the bones and parathyroid glands of persons with hyperthyroidism (1). Robertson (38) reports that the thyroxin lowers the calcium threshold by direct tubular influence and thus causes hypercalciuria.

Determination of phosphate clearance and the tubular reabsorption of phosphate as indication of the parathyroid function in thyroid disorders has been carried out in only a few isolated cases. Kyle et al. (26) have reported, without giving full experimental details, that phosphate clearance may be increased in hyperthyroidism, whereas Nordin et al. (35) state that this may be reduced in some instances.

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MATERIAL AND METHODS

The study includes 27 patients with hyperthyroidism, seven with primary myxoedema, two euthyroid patients with malignant exophthalmus and four with hypopituitarism. None had roentgenological bone changes, probably because of the short duration of the disease. The following examinations were performed: — measurement of basal metabolic rate, determination of protein-bound iodine in serum a. m. Barker (3), measurement of uptake of labelled l-triiodothyronine in the erythrocytes incubated with patient's plasma (13), and determination of serum phosphate (31), alkaline phosphatase (23), serum calcium and urine calcium after intake of ordinary food (EDTA method (28)). Where the urine calcium level was higher than 300 mg per day, the determinations were made after intake of calcium restricted diet. The values were then less than 150 mg per day in normal persons (16).

Further, phosphate clearance, creatinine clearance and tubular reabsorption of phosphate as percentage of the amount of glomerular filtration, were measured, as described in a previous work (14). The study periods were from 9 a.m. to 1 p.m. and from 1 p.m. to 5 p.m.

$$\text{Phosphate clearance ml/min.} = \frac{\text{Diuresis} \times \text{urine phosphate in mmol/l.}}{240 \times \text{serum phosphate in mmol/l.}}$$

$$\text{Creatinine clearance ml/min.} = \frac{\text{Diuresis} \times \text{urine creatinine in mg/100 ml}}{240 \times \text{serum creatinine in mg/100 ml}}$$

and

$$\text{Tubular reabsorption of phosphate as percentage of amount of glomerular filtration (TRP \%)} = \left(1 - \frac{\text{urine phosphate in mmol/l.} \times \text{serum creatinine in mg/100 ml}}{\text{serum phosphate in mmol/l.} \times \text{urine creatinine in mg/100 ml}}\right) \times 100\,\%$$

Phosphate was determined a. m. Müller (31) and creatinine a. m. Bonsnes & Taussky (7).

Table 1.
Phosphate Clearance and Percentage Tubular Reabsorption of Phosphate (TRP per cent) in 27 Patients with Hyperthyroidism.

No.	Sex	Age	BMR (-10-+10 per cent)	PBI (3.0-8.0 μg/100 ml)	T_3-uptake in red cells (6.0-10.5 per cent)	Serum calcium (4.5-5.5 meq/l)	**Serum phosphate (0.9-1.5 mmol/l)	*Urine calcium (150-300 mg/day)	**Phosphate clearance (6.0-15.0 ml/min)	**Creatinine clearance (>67 ml/min)	**TRP per cent (83-93 per cent)	TRP per cent during Ca infusion	TRP per cent after Ca infusion
1	W	42	+100	18.9	20.8	5.1	1.73	253	10.5	62.9	83.7		
2	M	46	+ 88	16.0	20.2	5.4	2.16	569—394	21.7	179.0	86.6		
3	W	22	+ 83	18.4	20.6	6.7	0.92	1182—725	34.9	87.6	59.1	77.1	79.0
4	M	50	+ 83	14.4	11.4	4.3	1.25	279	4.9	42.7	82.4		
5	W	57	+ 82	10.9	20.1	—	1.40	357—216	7.4	44.7	83.2		
6	W	45	+ 68	17.8	17.2	4.8	1.27	615—332	13.7	146.8	91.2		
7	W	48	+ 64	8.2	11.7	4.4	0.99	220	7.7	76.1	89.7		
8	M	18	+ 57	19.1	17.1	6.3	2.01	1085—789	17.3	74.5	79.9	80.7	79.1
9	M	55	+ 57	11.8	12.6	4.6	0.87	165	9.1	84.1	89.2		
10	M	55	+ 55	17.0	21.2	4.8	1.00	102	6.3	61.9	89.8		
11	M	59	+ 52	11.3	15.4	—	1.33	579—538	14.4	105.6	83.1	86.1	84.8
12	W	44	+ 49	8.3	10.8	4.9	1.62	336	7.1	65.0	89.1		
13	W	48	+ 48	8.9	8.6	4.8	1.22	492—459	18.2	96.7	81.1	88.2	82.6
14	W	48	+ 48	9.0	11.4	4.6	1.33	247	16.6	106.2	84.4		
15	M	61	+ 47	10.6	9.2	5.2	1.29	305	16.9	124.7	84.8	93.8	93.2
16	W	40	+ 47	5.2	17.2	4.9	1.32	294	17.6	142.9	87.3		
17	W	62	+ 47	—	15.6	4.7	1.34	274	13.0	89.2	85.3	89.4	85.9
18	W	76	+ 44	13.2	11.1	4.4	1.05	190	32.4	157.8	79.4		
19	W	50	+ 44	9.2	10.7	4.7	1.25	396	13.9	83.3	83.2		
20	W	34	+ 40	—	12.2	4.9	1.67	800—530	25.8	121.1	79.3	92.9	87.2
21	W	21	+ 38	7.1	16.1	4.4	1.63	509	12.4	89.5	89.6		
22	W	54	+ 34	8.6	—	5.2	1.00	461—349	23.5	126.8	81.4	84.4	90.5
23	W	68	+ 32	9.8	14.5	4.9	1.22	196	11.3	78.2	85.5		
24	W	46	+ 32	8.7	9.8	4.7	1.25	126	6.1	73.5	91.7		
25	W	61	+ 30	18.8	8.4	4.6	1.02	—	8.2	57.8	85.3		
26	W	70	+ 29	11.4	12.9	4.6	1.60	77	10.5	85.7	87.8		
27	W	46	+ 23	8.5	14.0	4.5	1.16	293	11.1	58.8	81.2		

*) The first of the two figures in the column "Urine calcium" indicates the excretion after ordinary food and the second the excretion after calcium restricted food.
**) The figures are the means of two daily determinations.

RESULTS

1. *Hyperthyroidism.*

The results of examination of the 27 patients with hyperthyroidism are shown in Table 1, which gives the mean values of the two determinations (i. e. 9 a. m. — 1 p. m. and 1 p. m. — 5 p. m.) of phosphate and creatinine clearance and TRP%. The order of the patients is according to decreasind basal metabolic rate, which varied from +100 per cent to +23 per cent. The PBI was increased in all cases except two (Nos. 16 and 21). Two patients were given roentgen contrast containing iodine and therefore the PBI values could not be used (Nos. 17 and 20). Triiodothyronine uptake by the erythrocytes was increased in 22 cases and normal in 4 (Nos. 13, 15, 24 and 25). The test was not made in one case (No. 22).

The serum calcium values were normal in all cases except two, where they were increased (Nos. 3 and 8) and four, where they were slightly reduced (Nos. 4, 7, 18, 21). The serum phosphate concentration was normal in 19, was increased in 7 (Nos. 1, 2, 8, 12, 20, 21, 26) and was slightly reduced in one (No. 9).

Urine calcium excretion was increased in 13 out of 26 patients (Nos. 2, 3, 5, 6, 8, 11, 12, 13, 15, 19, 20, 21, 22). It was not possible to demonstrate any definite relationship between this and the concentration of calcium and phosphate in serum, the basal metabolic rate, the PBI or the triiodothyronine uptake by the erythrocytes. However, the two patients with pronounced hypercalciuria (Nos. 3 and 8) had increased serum calcium. Twelve patients (Nos. 4, 6, 7, 8, 13, 14, 15, 16, 19, 22, 23, 27) had increased alkaline phosphatases in serum.

The phosphate clearance was unusually high in 10 patients (Nos. 2, 3, 8, 13, 14, 15, 16, 18, 20 and 22). However, comparison between phosphate and creatinine clearance showed a definite relationship, as also demonstrated in a previous work (14) (Fig. 1). A few of the patients with hyperthyroidism had high creatinine clearance, without it being possible to find any definite rela-

tonship between these values and the basal metabolic rate (Fig. 2), which agrees with the findings of Bartels (4). Other authors have reported increased glomerular filtration in thyrotoxicosis (22, 30).

The tubular reabsorption of phosphate, which was independent of the size of creatinine clearance (Fig. 3), was reduced in eight of the patients (Nos. 3, 4, 8, 13, 18, 20, 22 and 27). It was shown that increased basal metabolic rate and increased PBI had a tendency to decrease the TRP % (Figs. 4 and 5) while, strangely enough, no relationship could be found between the triiodothyronine uptake by the erythrocytes and the TRP %. There was no connection between serum phosphate and serum calcium on the one hand and the TRP % on the other. However, the two patients with increased serum calcium had reduced TRP %. The finding that there was no definite relationship between the TRP % and serum phosphate is in agreement with the results of a previous work (14) and of a study by Reiss et al. (37).

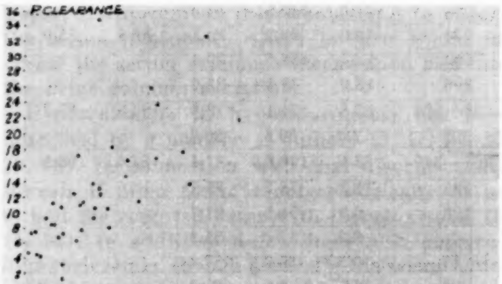


Fig. 1.

Relationship Between Phosphate and Creatinine Clearance in Hyperthyroidism and Hypothyroidism.

Abscissa: Creatinine clearance in ml per minute.
Ordinate: Phosphate clearance in ml per minute.

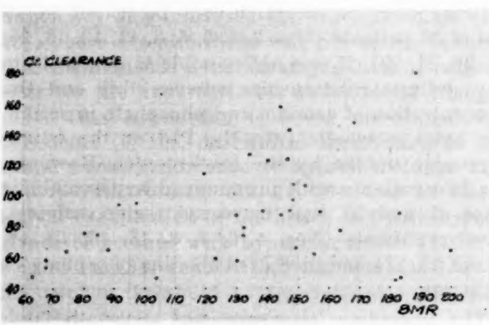


Fig. 2.

Relationship Between Basal Metabolic Rate and Creatinine Clearance in Hyperthyroidism and Hypothyroidism.

Abscissa: Basal metabolic rate as percentage of normal.
Ordinate: Creatinine clearance in ml per minute.

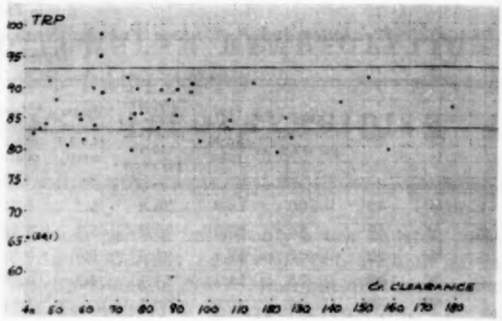


Fig. 3.

Relationship Between Creatinine Clearance and Tubular Reabsorption of Phosphate in Hyperthyroidism and Hypothyroidism.

Abscissa: Creatinine clearance in ml per minute.
Ordinate: Tubular reabsorption of phosphate as percentage of the amount of glomerular filtration.

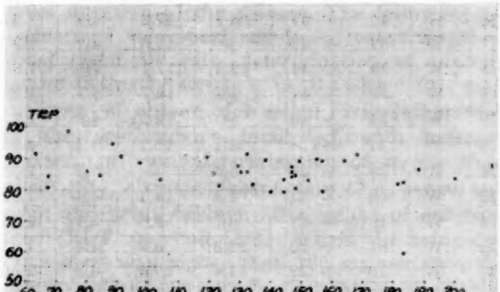


Fig. 4.

Relationship Between Basal Metabolic Rate and Tubular Reabsorption of Phosphate in Hyperthyroidism and Hypothyroidism.

Abscissa: Basal metabolic rate as percentage of normal.
Ordinate: Tubular reabsorption of phosphate as percentage of the amount of glomerular filtration.

It was found that increased urine calcium excretion was connected with falling TRP % (Fig. 6). However, eight out of 13 patients with hypercalciuria had normal TRP % and three out of eight with reduced TRP % showed no increase of urine calcium.

Calcium infusion was carried out in eight patients (Nos. 3, 8, 11, 13, 15, 17, 20, 22) with 15 mg calcium per kilogram of body weight, as described previously (14). Of these, five had reduced TRP %. In all cases a varying increase in the TRP % took place, except in one patient (No. 8) where there was hardly any change. The reason for the rise is presumably that the increased calcium concentration in the blood inhibits the parathyroid function (34).

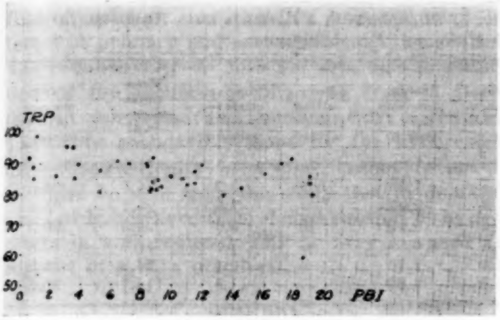


Fig. 5.

Relationship Between Concentration of Protein-bound Iodine in Serum and Tubular Reabsorption of Phosphate in Hyperthyroidism and Hypothyroidism.

Abscissa: Concentration of protein-bound iodine in serum in μg %.

Ordinate: Tubular reabsorption of phosphate as percentage of the amount of glomerular filtration.

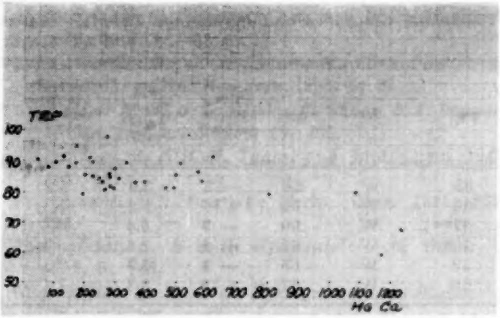


Fig. 6.

Relationship Between Renal Calcium Excretion and Tubular Reabsorption of Phosphate in Hyperthyroidism and Hypothyroidism.

Abscissa: Renal calcium excretion in mg pr. 24 hours.

Ordinate: Tubular reabsorption of phosphate as percentage of the amount of glomerular filtration.

2. *Hypothyroidism.*

The results of the examination of the seven patients with clinically typical myxoedema can be seen from Table 2. All had reduced basal metabolic rate and five had reduced protein-bound iodine (Nos. 28, 30, 31, 32, 33) but only three (Nos. 28, 29, 30) showed reduced uptake of l-triidothyronine by the erythrocytes. They all had normal serum phosphate, serum calcium and urine calcium excretion, except one (No. 33) where the value for the lastnamed test was increased after intake of normal diet. The phosphate clearance was reduced in three (Nos. 28, 31, 32) but the creatinine clearance was low in these patients, as also in patients 29 and 30. This condition has previously been described in patients with myxoedema (5, 22, and others). A definite correlation could be demonstrated between the creatinine clearance and the basal metabolic rate. This is in contrast to what is found in hyperthyroidism (Fig. 2), a fact to which M c K a y et al. (30) have drawn attention from the point of view of urea clearance.

The tubular reabsorption of phosphate was normal in all patients except two (Nos. 29 and 32), where it was reduced in the first case and increased in the second. Calcium infusion was performed in the patient with increased TRP % (No. 32), with the result that the TRP % fell. This finding is observed in patients with hypoparathyroidism (34).

3. *Hypopituitarism and malignant exophthalmus.*

This group included six patients, four with hypopituitarism (Nos. 35, 36, 37, 38, Table 3) and two euthyroid patients with malignant exophthalmus (Nos. 39 and 40). Two of the patients with hypopituitarism had not been treated (Nos. 35 and 36). Both had clinical symptoms of hypothyroidism and had reduced excretion of pituitary gonadotrophin and 17-ketosteroids in the urine. No. 35 had also symptoms indicating

Table 2.

Phosphate Clearance and Percentage Tubular Reabsorption of Phosphate in 7 Patients with Primary Myxoedema.

No.	Sex	Age	BMR (-10-+10 per cent)	PBI (3.0-8.0 μg/100 ml)	T_3-uptake in red cells (6.0-10.5 per cent)	Serum calcium (4.5-5.5 meq/l)	**Serum phosphate (0.9-1.5 mmol/l)	Urine calcium (150-300 mg/day)	**Phosphate clearance (6.0-15.0 ml/min)	**Creatinine clearance (>67 ml/min)	**TRP per cent (83-93 per cent)
28	W	64	—37	0.5	5.1	4.9	1.02	213	4.3	47.7	91.1
29	W	60	—33	5.2	5.0	4.8	1.10	268	9.1	53.6	80.4
30	W	71	—33	0.8	4.7	4.9	1.12	226	8.4	58.2	84.9
31	W	71	—	0.8	7.2	—	1.06	145	4.1	50.0	88.0
*)32	W	46	—26	1.0	7.7	5.1	1.14	271	1.1	64.9	98.2
33	M	61	—20	2.3	8.7	4.6	0.94	490	10.9	75.4	85.4
34	M	56	—16	3.6	7.8	5.0	1.22	275	12.3	73.9	84.9

*) Calcium infusion was carried out in patient nr. 32, with the result that the TRP per cent during and after the test was 90.8 per cent and 98.3 per cent.

**) The figures are the means of two daily determinations.

Table 3.

Phosphate Clearance and Percentage Tubular Reabsorption of Phosphate in 4 Patients with Hypopituitarism (no. 35—38) and 2 Patients with Malignant Exophthalmus.

No.	Sex	Age	BMR (-10-+10 per cent)	PBI (3.0-8.0 μg/100 ml)	T_3-uptake in red cells (6.0-10.5 per cent)	Serum calcium (4.5-5.5 meq/l)	*Serum phosphate (0.9-1.5 mmol/l)	Urine calcium (150-300 mg/day)	*Phosphate clearance (6.0-15.0 ml/min)	*Creatinine clearance (>67 ml/min)	*TRP per cent (83-93 per cent)
35	W	56	—12	3.0	5.2	4.7	1.45	165	3.2	64.5	94.9
36	W	62	+19	1.2	7.0	4.9	0.95	—	7.6	24.1	65.4
37**)	W	60	— 9	3.4	—	4.6	1.12	40	8.0	94.3	90.3
38**)	W	67	+ 4	8.6	—	4.5	0.88	—	7.6	46.8	83.8
39	W	63	— 3	3.8	6.5	4.4	1.16	—	10.4	94.2	89.0
40	W	41	+19	6.3	7.4	4.7	1.09	—	11.3	114.7	90.3

**) Treated with des. Thyroid and Cortisone.
*) The Figures are the Means of two Daily Determinations.

diabetes insipidus. The two other patients (Nos. 37 and 38) were being treated with desiccated thyroid and cortisone.

The one untreated patient with hypopituitarism (No. 35) had reduced phosphate clearance and increased TRP %, thus suggesting impaired parathyroid function. However, serum calcium and phosphate concentration were normal. The case of patient No. 36 was difficult to evaluate on account of renal failure which was accompanied by reduced TRP % (14). Phosphate clearance and TRP % values were normal in the two treated patients.

The two patients with malignant exophthalmus (Nos. 39 and 40) had normal phosphate clearance and TRP %.

Discussion and Conclusion.

This study has shown that patients with hyperthyroidism may have reduced tubular reabsorption of phosphate (Nos. 3, 4, 8, 13, 18, 20, 22, 27. Table 1), possibly indicating increased parathyroid function. The opposite was found in two patients with hypothyroidism (Nos. 32 and 35), which probably indicates decreased parathyroid function, but one (No. 29) had reduced TRP %. However, there were no definite clinical signs of hyperparathyroidism or hypoparathyroidism in these 11 patients with abnormal TRP %. As regards the patients with hyperthyroidism (Table 1), there were no definite roentgenological skeletal changes, but as the disease was of short duration in all cases (up to one year), this provides no absolute evidence. Five of the eight patients with reduced TRP % had hypercalciuria (Nos. 3, 8, 13, 20, 22. Table 1), but this symptom could be seen in eight with normal TRP % (Nos. 2, 5, 6, 11, 12, 15, 19, 21). Two of the patients with reduced TRP % had increased serum calcium (Nos. 3 and 8); this could not be found in any of the other patients. Five of the patients with reduced TRP % had increased concentration of alkaline phosphatases (Nos. 4, 8, 13, 22, 27), but seven with normal TRP % also showed the same symptom (Nos. 6, 7, 14, 15, 16, 19, 23). Seven had increased serum phosphate (Nos. 1, 2, 8, 12, 20, 21, 26) and this value was decreased in one (No. 9). Only two of these patients (Nos. 8 and 20) had reduced TRP %.

In this connection, the studies of Engfeldt & Hjertquist (10) on rats and dogs are of interest. They demonstrated that thyreotropic hormone used in animal experiments caused histological signs of hyperfunction of both the thyroid and the parathyroid glands with increase of serum phosphate and renal phosphate excretion. Those authors are of the opinion that injection of TSH primarily causes hyperfunction of the thyroid gland and increasing serum phosphate, which secondarily releases hyperparathyroidism. Similar findings have been observed in the treatment of rats with thyroxin (9). However, among the patients in the present study, only seven had increased serum phosphate and only two of these had reduced TRP%. This does not support the theory that increased serum phosphate causes increased parathyroid function in these patients. No satisfactory explanation is available as to why hyperthyroidism may be accompanied by increased concentration of serum phosphate.

The fact that hyperthyroidism may be accompanied by reduced tubular phosphate reabsorption may also be because the thyroid hormone directly inhibits the tubular reabsorption of phosphate. Beisel et al. (5) and Hetzel et al. (21), in experiments on humans and dogs, have demonstrated that triiodothyronine increases the phosphate clearance in the course of a few hours. However, the studies do not exclude the possibility that the course of this effect may be via the parathyroid gland. The fact that in four out of five patients with hyperthyroidism and reduced TRP % calcium infusion caused the latter value to increase might support the theory that the reduced TRP % is actually due to hyperparathyroidism. Were the thyroid hormone responsible for the reduced TRP % by means of direct tubular effect, it could hardly be expected that calcium infusion would normalize the parameter.

It can be concluded that in hyperthyroidism there is often reduced tubular reabsorption of

phosphate measured as the percentage of the filtered amount, and that the opposite may be found in primary and secondary hypothyroidism. The reduced TRP % does not give rise to reduction of the serum phosphate as seen in parathyroid adenoma, and neither can a reduced TRP % be responsible alone for the hypercalciuria, though it may be a contributory factor. It will also be seen from the study that in doubtful cases of hyperthyroidism demonstration of hypercalciuria and reduced TRP % may be used in support of such a diagnosis.

SUMMARY

Phosphate clearance and the tubular reabsorption of phosphate as percentage of the amount of glomerular filtration was determined in 27 patients with hyperthyroidism, seven with primary myxoedema, two euthyroid patients with malignant exophthalmus and 4 with hypopituitarism (two under treatment). The tubular reabsorption of phosphate was reduced in eight of the patients with hyperthyroidism, probably indicating increased function of the parathyroid gland. Five of these had hypercalciuria and two hypercalcaemia. Falling TRP % was connected with increased urine calcium excretion.

Increased tubular reabsorption of phosphate was found in one patient with primary myxoedema and one with hypopituitarism, probably indicating a simultaneous reduction in the function of the parathyroid gland.

SUMMARIO

Thorkild Friis: CLEARANCE DE PHOSPHATO E REABSORPTION TUBULAR DE PHOSPHATO IN PATIENTES CON HYPERTHYROIDISMO E HYPOTHYROIDISMO

Esseva determinate le clearance de phosphato e le reabsorption de phosphato in termino del percentage del filtration glomerular in 27 patientes con hyperhyroidismo, 7 con myxedema primari, 2 patientes euthyroide con exophthalmia maligne, e 4 con hypopituitarismo (duo sub tractamento). In octo del paientes co nhyperthyroidismo le reabsorption tubular de phosphato esseva reducite, probabilemente como indicio de un function augmentate del glandula parathyroide. Cinque inter illes habeva hypercalciuria e duo hypercalcemia. Diminution del RTP % esseva connectite con excretion augmentate de calcium in le urina.

Augmentate reabsorption tubular de phosphato esseva trovate in un patiente con myxedema primari e in un con hypopituitarismo, probabilemente como indicio de un reduction simultanee del function del glandula parathyroide.

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HYPERGLYCEMIA AS THE CAUSE OF CHARACTERISTIC FEATURES OF THE FOETUS AND NEWBORN OF DIABETIC MOTHERS

By JØRGEN PEDERSEN and MOGENS OSLER

Newborn infants of diabetic mothers (infants of diabeticae) show characteristic deviations from the normal, among which a high perinatal mortality, a high birth weight, hypertrophy of the islet tissue of the pancreas, a large diuresis, loss of weight during the first neonatal days, increased extramedullary hæmopoiesis, and neonatal hyperbilirubinæmia are the most conspicuous. Further the baby may be hypoglycemic during the first 24 hours of life, but neonatal hypoglycemia is not in itself a cause of death according to general opinion (see *e.g.* Pedersen 1952).

The discussion of the pathogenesis of the characteristic features has been dominated by four hypotheses: the hyperglycemia, the growth-hormone, the hyperadrenocorticism, and the genetic hypothesis.

The hypothesis of hyperglycemia-islet-cell hypertrophy-hyperinsulinism was developed in the 1920's (Dubreuel and Anderodias) and at present reads as follows: Maternal hyperglycemia results in fetal hyperglycemia and hence in hypertrophy of fetal islet-tissue. This again means a greater secretion of fetal insulin and a greater utilization of the glucose received from the mother. The baby therefore grows larger and fatter than normal and the newborn infant tends to be hypoglycemic because of an increased secretion of insulin, continued after birth for some time.

In a previous publication (Pedersen 1952) the plausibility of this hypothesis was discussed at some length. Suffice it here to mention that the fetus of a diabetic mother receives a constant infusion with an increased but fluctuating glucose content, that glucose is the adequate stimulus for secretion of insulin, that the hormones, *in casu* insulin, are secreted and work in foetal life and that the infants of diabetic mothers as a group have a pronounced increase of the islet tissue (Cardell 1953, Driscoll et al. 1960) due to an increase both in number and in size of the islets. This hypertrophy of islet tissue has been noted as early as in the fourth lunar month (Gayer & Staeffen 1957).

That there is no general agreement upon this simple — and thus attractive — hypothesis is due not so much to the fact that an increased insulin-activity has not been measured in these infants up till now, as to the apparent incompatibility of the hypothesis with the fact that women who develop diabetes mellitus at a later date often give birth to large infants years before the diabetes is diagnosed. Further, the islet-tissue hypertrophy is said to be found also in babies dying from rhesus-incompatibility (Miller et al. 1944, Cardell 1953).

It is the purpose of this paper to define the limits of the old hyperglycemia hypothesis as elucidated by a short survey of the major findings of our continued studies of this problem and by a discussion of the four hypotheses in the light of the total body of results and findings in the literature.

Royal Maternity Department B, Rigshospitalet, Copenhagen. (Head: Professor *E. Brandstrup*).

FINDINGS

A. *The blood sugar during fasting in the first 24 hours of life.*

The blood sugar (capillary blood, Hagedorn-Jensen method) was measured four times a day at fixed hours in 18 diabetic mothers during their last stay in the department during pregnancy. The duration of this stay ranged from 32—80 days (long-term treatment) averaging 52 days. The mean of each mother's blood sugar was computed and in the 18 cases this "pregnancy level" of the blood sugar varied from 108—167 mg/100 ml, averaging 134 mg/100 ml. In their 18 fasting babies duplicate samples of capillary blood for blood sugar determination were taken from the heel four to 12 times

Figure 1.

Relation Between Blood Sugar Levels During Last Part of Pregnancy in 18 Long-term Diabetics and Those of Their Infants During First 24 Hours of Life.

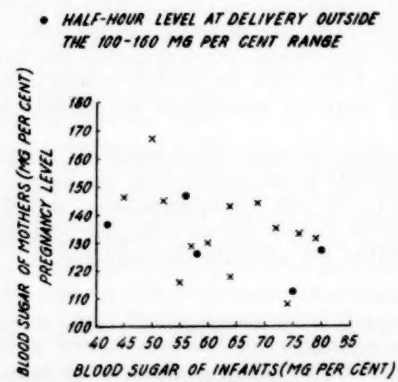


Table 1.
Body Composition of Diab. Infants, Normal Full-term, Control Infants and Premature Infants.

	Diab. infants	Normal infants	Control infants	Premature infants
Body weight (BW) (g)	3,500	3,300	2,700	2,100
Total body water (per cent of BW)	70.2	78.2		
Extracellular water (per cent of BW)	38.5	44.9		
Intracellular water (per cent of BW)	31.8	33.5		
Lacking superior tibial epiphyseal center (in per cent of cases)	44	0	30	100
Thickness of subcutaneous fat (mm)	11.2	8.1	7.5	4.5
Water excretion (first 48 hours, ml)	107	56		95
Nitrogen excretion (first 48 hours, mg)	500	370		530

(averaging 6.8 times) during the first 24 hours of life. For each infant the average blood sugar "the 24-hour-level" was computed, varying from 46 to 96 mg/100 ml (on average 66 mg/100 ml).

From Figure 1 is seen that a negative correlation exists between the mother's "pregnancy-level" and the baby's "24-hour-level" of blood sugar. Besides a positive correlation exists between the infant's "24-hour-level" and the mother's mean blood sugar at delivery, but this correlation does not influence the blood sugar of the infants as much as does the maternal "pregnancy level" (for formula of regression lines and coefficients see Pedersen 1952).

Thus we have found that the infant's blood sugar during the first 24 hours is the higher the lower the mother's blood sugar is kept during the latter part of pregnancy. This finding fits the hyperglycemia hypothesis.

B. *The body composition of newborn infants of diabetic mothers.*

Osler (1960 a, b, c) determined the body composition of newborn infants of diabetic mothers by measuring total body water, extracellular and intracellular water, body fat, urinary excretion of water, nitrogen and electrolytes and Pedersen and Osler (1958) the maturity, judged by osseous development. A summary of the results is given in Table I. The result of the investigations is that these infants must be characterised as infants whose maturity in terms of development of ossification centres, water, electrolyte and nitrogen excretion and other organ functions corresponds to their chronological age, or even less. They are premature. Besides they are grossly overweight on account of a surplus of fat and carbohydrate stores in tissues and organs. The water content is low. Obesity and increased glycogen stores were to be expected if the maternal hyperglycemia is followed by fetal hyperglycemia and hyperinsulinism. In other words this result strongly supports the hyperglycemia hypothesis. Little is known about hormonal influence on maturity, but presumably glucose + insulin increases the fat and glycogen content of the body without accelerating ossification; the results once more fitting the hyperglycemia hypothesis.

C. *The blood sugar level in mothers with large infants.*

One of the most thorough direct examinations of the blood sugar during and outside pregnancy has been made by Hagen (1958). The oral and intravenous glucose tolerance tests and the fasting blood sugar and the tolerance curves during women, a group with babies of normal birth weight and a group with large babies. The fasting blood sugar and the tolerance curves during pregnancy showed alterations in the same direction in the two groups, but one essential difference was seen. The mothers of large babies had a higher blood sugar level outside and inside pregnancy, fasting as well as at any point of time during glucose tolerance tests. This is seen in Figure 2. It means that, on average, a large foetus has been fed more glucose during pregnancy than a foetus of a mother, who does not bear large infants.

This hyperglycemia, although slight, might be the simple explanation of the large size of infants in the "prediabetic" period of diabetic women. Babies born in the diabetic and the "prediabetic" period have the same pathology—*e. g.* large size and hyperplasia of the islet-tissue—and the same primary cause: hyperglycemia.

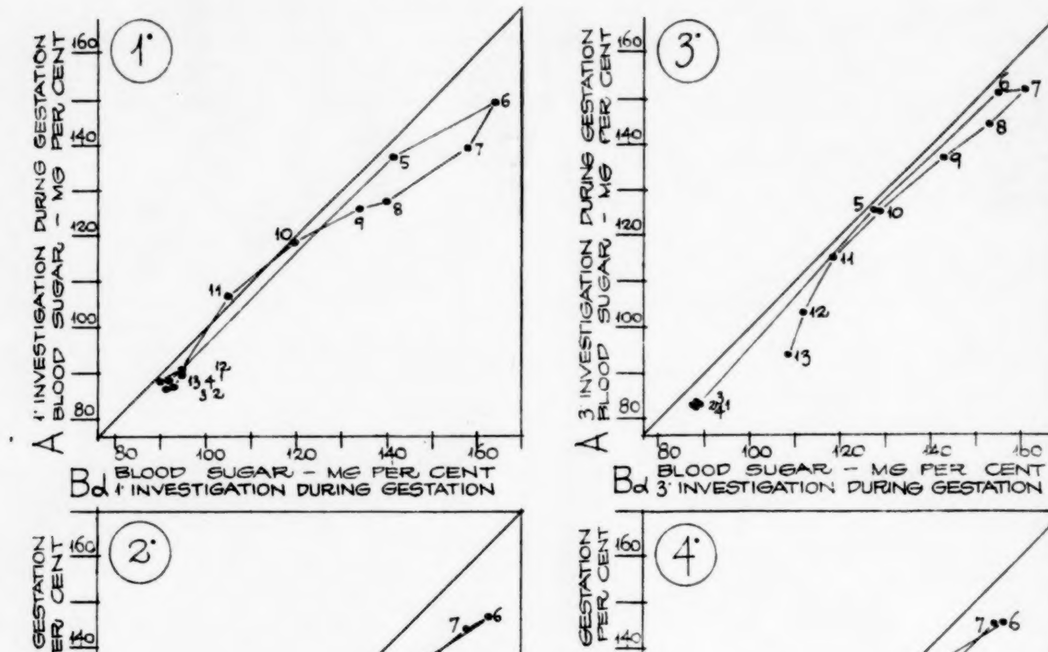
These findings would appear to remove one of the main obstacles for the acceptance of the hyperglycemia hypothesis.

DISCUSSION

As mentioned we shall discuss the total results of clinical investigations of the subject in relation to the four advanced hypotheses. At the present moment, however, the problem of congenital malformations in infants of diabeticae is not so well elucidated that a discussion is worth while. Further, a discussion of the results of animal experiments is outside the scope of this paper. We refer to a recent publication (Osler 1961a).

I. *The growth hormone hypothesis.*

Growth hormone has a "diabetogenic effect" (Young 1944), and an overproduction of this



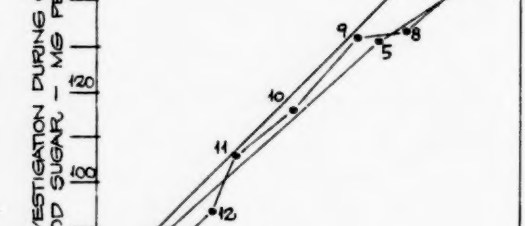


Figure 2.

The relationship between blood sugar values (fasting and after oral glucose-loading) on 4 different points of time during (No.s 1—4) and after pregnancy in two groups of women. Ordinates; average values from 28 women bearing infants of normal size; abscissae: average values from 13 women bearing large infants. On the curves the fasting blood sugar is point No. 1. Points 2—13 are the consecutive values from the oral glucose-loading test, determined every 20 minute.

Notice: at any point of pregnancy and outside pregnancy, the blood-sugar-loop is placed under the identity line, meaning that the blood sugar of the group of women with large babies always is the higher (from Hagen 1958).

hormone is thought to give rise to diabetes mellitus and to explain macrosomia of babies born by women as well in the years preceeding as after the diagnosis of diabetes. Further growth hormone overproduction is thought to give rise to the hyperplasia of the islets of Langerhans in the babies (Miller et al. 1944, and others).

However, many observations speak against this hypothesis. Although pregnancy is rare in acromegalic women, some 40—50 cases have been described in the literature (Abelove 1954, Jackson 1955), and there seems to be agreement about the observations that acromegalic women neither give birth to many still-born babies, nor to many large babies. This speaks against any influence of maternal growth hormone on the birth weight of the baby. Moreover, growth hormone is a high molecular protein which only very slowly passes the placenta (Page, 1958). The finding of marked insular hyperplasia in malformed diabetic foetuses with a disturbed hypothalamo-hypophyseal system further excludes participation of foetal pituitary growth hormone or adrenocorticotrophic hormone in this feature (Driscoll & Benirschke, in preparation).

Finally most of the pathologic findings in infants of diabeticae cannot easily be explained by the growth hormone hypothesis or are even incompatible with this hypothesis, *e.g.* the blood sugar relationship in the first 24 hours of life and the development of ossification centres in such infants. The results of the investigations of the body composition are completely incompatible with a somatotrophic influence according to our present knowledge.

II. *The hyperadrenocorticism hypothesis.*

Some diabetic infants have an appearence somewhat similar to that seen in adult patients with Cushing's syndrome. They are hairy with round, red faces and swollen cheeks, the "tomatolike" face.

Hoet (1954) found corticosteroids in the amniotic fluid from one pregnant diabetic patient, but not in amniotic fluid from normal patients, and Bjørklund (1954) and Farquhar (1956) found increased urinary excretion of 17-ketosteroids and acid-stable formaldehydrogenic steroids, respectively, in the neonatal period of infants of diabeticae. Hence it was thought that their pathology might be explained by hyperadrenocorticism.

It will be seen below, however, that this hypothesis is not very well founded and fails to explain essential points.

Pregnancy in mothers with active Cushing's disease is extremely rare, but in the few cases reported, no especially large babies were born. (Hunt & McConahey, 1953, Jackson 1955). Further, Driscoll et al. (1960) failed to corroborate earlier reports of increased adrenal weight in infants of diabeticae. Baird & Bush (1960) failed to find any difference between the cortisol and cortisone content of amniotic fluids from normal and diabetic mothers. Migeon et al. (1960) determined 17-hydroxycorticosteroids in plasma from maternal venous blood of 13 diabetic mothers and in cord venous blood of their infants at the time of elective Caesarean section. No significant differences were found between plasma levels when compared with normal controls. These investigations speak against the concept that hyperfunction of the adrenal cortex in mother or fetus might be the primary factor in the pathology of infants of diabeticae.

However, as to some extent insulin and glucocorticoids act in an antagonistic manner in carbohydrate metabolism, the hyperinsulinism might give rise to a secondary compensatory rise in glucocorticoid-production, but so far we have no evidence of this.

III. *The genetic point of view.*

In 1954 Jackson presented data indicating that the birth-weights of infants of diabetic fathers were above average, whereas the stillbirth rate of such infants was not increased. These data suggested in Jackson's opinion, that the onus of production of large babies cannot be borne entirely by maternal factors, but must in part be an inheritated phenomenon, linked in some way to the diabetic genetic constitution of either parent (see also Pirart 1955). However, similar investigations of Babbott et al. (1958) could not confirm Jackson's results. Babbott et al. found no difference in perinatal mortality or birth-weight between infants born of diabetic and non-diabetic fathers. In a study of 100 infants of diabeticae, whose ancestors (including the father and his family) included other diabetics than the mother, Nygård et al. (1961) were unable to find significantly higher perinatal mortality than among infants, whose ancestors did not include other diabetics than the mother. Nor was there any difference between the birth-weight of these two groups of infants (unpublished data.)

There may be a genetic link between large babies and diabetes, but this has not been proved, and even so the findings, *e.g.*, the blood sugar correlations of mother and infant, and the infant's body composition cannot easily be explained without applying the hyperglycemia hypothesis.

IV. *The hyperglycemia hypothesis.*

Our major findings fit the hyperglycemia hypothesis only. But does hyperglycemia explain all of the characteristic features of the foetus and newborn?

Pedersen (1952) found, that the larger the infant the lower was the blood sugar during the

first 24 hours, and Cardell (1953) and Driscoll et al. (1960) both found a positive correlation between the amount of islet tissue and the birth-weight of the infant. These findings fit the hypothesis well.

Osler (1961 b) found that 20 babies of mothers with Addison's disease weighed 3050 g (mean) at birth and thus were 500 g lighter than control infants. However, we have observed a patient with Mb. Addison and diabetes mellitus who gave birth to a very heavy baby weighing 4750 g (Osler & Pedersen 1961). Only two similar cases have been reported (Gurling et al. 1954, Rambert & Hervé 1960), and the mean birth-weight of the three infants of Addisonian + diabetic mothers born near term was 4400 g. The large difference in birth-weight between infants born of Addisonian and Addisonian + diabetic women indicates that the pregnancy level of glucose (*vide supra*) is the determining factor of the infants' birth-weight in these cases.

In a study from 1954 Pedersen found that a group of infants of diabetic mothers receiving long-term treatment during pregnancy (and thus on average having a lower pregnancy level of the blood sugar) had a lower birth weight than a comparable group of infants, whose mothers had short-term treatment during pregnancy. This difference of weight, however, was not statistically significant. In the belief that this might be due to the small size of the material a new comparison was made when the material had doubled (not published). The difference between long-term and short-term infants was of the same magnitude as earlier (average 150 g) but still not statistically significant. We are of the opinion that this results does not definitely speak against the hyperglycemia hypothesis and might be explained by one or more of the following points: (1) Long-term treated mothers are lying down for much more time during the latter part of pregnancy, a position that will tend to make the babies bigger and so oppose the weight-reducing effect of the long-term treatment. (2) The long-term treatment reduces the severity of or postpone toxaemia, again tending to make the babies bigger and to oppose the birth-weight reducing intention. (3) The difficulty of being sure of having really comparable groups of any magnitude, because the status of the vessels and the complications of the mother seem to be of great importance.

In diabetic pregnancies delivery is most often artificially induced before term and the babies are not full-term at birth. Death *in utero* during the last months of pregnancy, suddenly and without demonstrable cause is characteristic, as is neonatal death under the picture of typical neonatal distress with atelectasis and hyaline membranes.

According to the investigations of the body composition, the infants can be characterized as being fat, glycogen-rich and immature. This triad makes it legitime to propose an explanation as well of the neonatal as the late intrauterine death.

The infants with cardio-pulmonary insufficiency display dyspnoea, tachypnoea shifting with periodic and shallow respiration, cyanosis, somnolence, retractions of the chest wall, low systemic pressure and arythmia, and if the baby lives long enough oedema is formed. The triad may initiate and must contribute to the maintenance of this distress. Obesity increases the resistance to movement of the chest bellows with all its consequences of alveolar hypoventilation. Here the analogy with the symptomatology of the ventilatory insufficiency seen in some very obese adults (Pickwick syndrome) is at hand; the significance of being fat is shown by the fact that slimming makes the insufficiency disappear (cf. Pedersen & Torp-Pedersen 1960). The burden of large fat depots which also have a great oxygen consumption may be too strenous and increase the immaturity of the newborn infant functionally. In connection with cardiac strain and immaturity the release of extra water following the breakdown of extra glycogen depots may explain the increased tendency to oedema, and when excreted be a contributory cause of the greater urinary output and neonatal weight loss seen in such infants (Osler & Pedersen 1958, Osler 1960 c).

Intrauterine death most probably is due to anoxia. Admittedly we have no direct measurements of an oxygen lack, but the characteristic increased extramedullary haematopoiesis found in diabetic infants born after 36 weeks only (Driscoll et al. 1960), at which period the frequency of intrauterine deaths rises—is strong indirect evidence. The cause of the supposed oxygen lack, is unknown; the enzymatic function of foetus or placenta may be deficient *(vide infra)*.

As oxygen deficiency stimulates the islet tissue to hyperplasia (Schlossmann 1938), the relative small insular hyperplasia seen in babies with haemolytic disease can be explained by oxygen deficiency.

The hyperbilirubinemia of infants of diabeticae may be explained by the combination of immaturity and increased haematopoiesis.

Testicular interstitial cell hyperplasia and luteinized ovarian cysts have been noted in many infants of diabetic mothers (Cardell 1953, Driscoll et al. 1960). The cause of this is the higher chorionic gonadotrophine level during diabetic pregnancy and thus is not incompatible with, although not explained by, the hyperglycemia hypothesis.

In the maternal organism the vessels are the site of an angiopathia diabetica, more or less pro-

nounced. A vascular abnormality may be present also in the placenta (Burstein et al. 1957), but in many investigations of the placenta nothing abnormal has been found. Presumably the cause of the increased incidence of toxaemia and hydramnios should be found in the placenta.

CONCLUSION

The cause of many features of the foetus and newborn infant of diabetic and "prediabetic" mothers is unknown, but it would appear that the well-founded hyperglycemia hypothesis can explain or contribute to the explanation of most of them, whereas any other forwarded hypothesis fail to explain essential points. The concept of hyperglycemia as a primary factor is still acceptable.

SUMMARIO

Jørgen Pedersen and *Mogens Osler:* HYPERGLYCEMIA COMO CAUSA DE TRACTOS CHARACTERISTIC DEL FETOS E NEONATOS DE MATRES DIABETIC

Super le base de nostre continue investigationes e illes de A. Hagen comparate con le litteratura le scopo de iste labor es le definition del limites del ancian hypothese de hyperglycemia contra le hypotheses del hormon de crescentia, del hyperadrenocorticalismo, e le hypothese genetic.

Le pathogenese de certe characteristicas del neonato diabetic es discutite in le lumine de trovatas concernente le nivello del sucro sanguinee in le neonatos e in le matres, e concernente le composition del texitos den neonato. Le characteristicas in question es alte mortalitate perinatal, alte peso natal, hypertrophia del insulas pancreatic, alte diuresis, diminution del peso durante le prime dies neonatal, augmentate hemopoiesis extramedullar, e hyperbilirubinemia neonatal.

Il es concludite que le cause de plure tractos charateristic del fetos e neonatos de matres diabetic o prediabetic os incognite, ma il es apparente que le hypothese hyperglycemic pote fornir le explanation total o partial del majoritate de iste tractos, dum omne altere hypothese proponite faille explanar punctos essential. Le concepto del hyperglycemia como factor primari es ancora acceptabile.

Our thanks are due to Dr. A. Hagen for permission to publish Fig. 2.

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GALLSTONE ILEUS

By OLAF AGNER, LEIF KULD HANSEN and OLE H. IVERSEN

Gallstone ileus is a comparatively rare but serious complication of gallstone disease. It is often difficult to diagnose gallstone ileus, and the rate of mortality is high.

Gallstone ileus has of course been described quite frequently in international literature, but so far relatively few large Danish series have been published.

As 17 cases of gallstone ileus have been recorded at the Municipal Hospital, Copenhagen, during the years 1944—1960, it is considered that an analysis of these cases may be of some interest.

During the period mentioned, a total of 396 patients were treated, who were suffering from ileus, *i. e.*, gallstone ileus was demonstrated in 4.3 per cent of all cases of ileus. Further, it may be stated that during the period mentioned 3575 patients with gallstone diseases received treatment in the two departments, *i. e.*, gallstone ileus was demonstrated in 0.46 per cent of all patients treated for gallstones.

Thirteen of the patients were women, 4 were men. The average age was 65.4 years (for women 63.1, for men 72.8 years).

Nine patients (7 women and 2 men) had previously shown symptoms of gallstones (from 4 months to 16 years prior to the ileus); 7 of these patients had had febrile attacks (cholecystitis?), 4 had had icterus (passage of stones?), 3 patients had previously been hospitalized, but none operated on. Eight patients, *i. e.*, almost half of the cases, had never shown symptoms of gallstones before.

Several of the 17 ileus patients had been ill for several days before the actual hospitalization, the shortest duration was 7 hours, and the longest 14 days, with an average of 4.2 days. All patients except one had had attacks of vomiting, 3 of them feculent. All patients except one had been suffering from abdominal pain, but in varying degrees; 8 patients complained of intermittent pain. In 5 of the patients the pain began under the right curvature, the others complained of diffuse abdominal pain. There were pain-free intervals in 6 cases; one patient had a pain-free interval of 2 days. A rise in temperature to 38—40 degrees was present in 10 patients. 16 patients had not defecated during 1 to 4 days, while 6 patients had no discharge of flatus. Two patients had a slight degree of icterus; there was no history of decolorized feces. In 8 patients the abdomen was soft, only slightly meteoristic, in the other patients there was some meteorism; a "taut" abdomen was found in only 4 cases. Four patients had tenderness under the right curvature, in 2 patients a distention was noticeable in the gallbladder region; in 2 patients there was "resistance".

Thirteen patients were X-rayed. In all 13 cases a straight X-ray was taken of the abdomen; in 12 patients this revealed a mechanical ileus in the small intestine, in 5 patients even gas in the deep biliary passages, and in 2 patients positive concrement shadows in the region of the small intestine. Four patients were further examined after administration of a contrast medium per os; in 2 of these patients negative stone shadows were demonstrated in the small intestine, and in one patient a fistula from the gallbladder to the duodenum. Three patients were given a contrast enema which in one patient revealed a negative stone shadow like a curved rarefaction in the contrast shadow. Prior to operation a diagnosis or a tentative diagnosis of gallstone ileus was made in 9 of the 13 X-rayed patients.

In one case the X-ray picture showed no abnormalities; the patient was operated on 7 hours later on the suspicion of appendicitis acuta; a green walnut sized gallstone was found distally in the ileum.

Fifteen of the 17 patients were operated on, 7 of them "shortly after hospitalization", one patient after 7 hours, but 7 patients only after an observation period of 1—3 days. Two patients underwent operation on the suspicion of appendicitis acuta without any pre-operative X-ray examination.

The findings during the operations were: in all cases obturating gallstones in the small intestine; in 3 patients in the jenunum, in 10 patients in the ileum, in 2 cases the localization was not stated.

The size of the stone is mentioned in 10 cases; they are described as "walnut-sized" to "green walnut-sized"; one of them, however, was "the size of a hen's egg". In 4 patients, 2 or more stones were found in the intestine, in 2 cases 2 stones the size of a walnut, in 2 cases one large and several small stones. In 14 cases the intestine was dilated, red, fibrin-covered proximal to the stone.

In 2 of the patients operated on there was a perforation between gallbladder and duodenum; in 4 other patients adhesions and distentions were found in the gallbladder region; in the remaining patients the region was not palpated. In

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all the cases the operation performed was an enterotomy with extirpation of the gallstones; there was no case of intestinal resection. In 6 cases there were post-operative complications owing to wound infections, in one case owing to wound rupture.

Three of the patients who were operated on died:

The Municipal Hospital, department V, case record no. 546/60.

76-year-old woman, previously well, hospitalized after 4 days of frequent vomiting, with discharge of hazel-nutsized gallstone per os. At hospitalization: weak, shocked, uraemic. S-creatinine 10.2 mg per cent. Electrocardiogram: sign of fresh coronary thrombosis; the abdomen soft with tender distention under right curvature; X-ray picture of the abdomen: mechanical ileus of the small intestine, and air in the biliary passages, as well as a round configuration in an air-filled loop of the small intestine. Attempts were made to improve the general condition by blood-transfusion, intravenous infusion of noradrenalin as well as digitalis. Owing to the coronary occlusion and shock condition the treatment was expectant, but as a repeated X-ray examination showed increasing ileus, the patient was operated on 2 days after hospitalization. A gallstone, the size of a hen's egg, was found in a loop of the small intestine; this stone was extirpated, and oral to this a pea-sized stone. The post-operative general condition was satisfactory, blood pressure 235/120, temperature normal. The electrocardiogram remained poor. 6 days after the operation the patient died suddenly.

Autopsy: embolia arteriae coronariae, cholecystitis, cholecysto- et choledocholithiasis, dilatatio ductus choledochi m. gr., cystis renis bilateralis m. gr.

There was no sign of a perforated gallbladder, and the large gallstone must have passed the enormously dilated ductus choledochus.

The Municipal Hospital, department V, case record no. 24/50.

71-year-old man; 4 months earlier gallstone attack with rise of temperature to 39 degrees. The present attack began 3 days before hospitalization with intermittent pain upwards in the abdomen, accompanied by frequent vomiting and nausea. No defaecation for 3 days, no flatus. General condition fairly good, temperature 36.8 degrees. There was no distention of the abdomen, but defence and tenderness of the right side are mentioned. An X-ray picture of the abdomen showed no sign of ileus or perforative peritonitis, only slight meteorism. As intraperitoneal inflammation was suspected, presumably appendicitis acuta, the patient was operated on 7 hours after hospitalization. The appendix was found to be normal; in the jejunum, about 40 cm from the duodenojejunal region, a green walnut-sized gallstone was found; the intestine oral to this region was somewhat dilated, covered with fibrin. The gallbladder was small and shrunken, surrounded by adhesions, but without any sign of fresh inflammatory changes. The palpated gallstone was extirpated by enterotomy. Post-operatively the patient was fidgety, delirious, shocked, increasingly uraemic. S-urea 200 mg per cent, S-creatinine 3.3 mg per cent, S-protein 8.0 per cent. The daily diuresis was kept at a level of barely 2000 ml, but in spite of transfusion and dextran infusion, the patient died in shock 4 days after the operation.

No autopsy was performed.

The Municipal Hospital, department V, case record no. 1785/44.

70-year-old woman, who had had a gallstone attack with rise of temperature 2 years earlier; not operated on. The present attack began 7 days before hospitalization with epigastric pain, temperature 39 degrees, nausea and feculent vomiting. No defaecation for several days, but discharge of flatus. The patient was slightly shocked, dehydrated. The abdomen soft, without soreness or abnormal distention, but ascites was suspected. The X-ray picture of the abdomen showed no sign of free gas or fluid level; after administration of a radiopaque meal it was observed to pass slowly through the small intestine. 48 hours later the abdomen was unchanged, soft, slightly meteoristic; repeated radioscopy showed that the contrast medium had passed down into the colon; numerous fluid levels were now visible in the small intestine, and a walnut-sized ring-formed shadow upwards on the right side of the abdomen. During the operation a green walnut-sized concrement was found in the ileum, which was distended oral to and shrunken anal to the concrement. The concrement was extirpated. The condition was satisfactory at the termination of the operation, but 3 hours later the patient suddenly became unconscious, with superficial respiration. The clinical picture resembled cerebral hemorrhage. The patient died 24 hours after the operation.

Autopsy: cholecystitis m. gr., empyema vesicae felleae, fistula cholecystoduodenalis (thrombosis aa. coron. vetus).

No autopsy of cerebrum.

Two patients were not operated on. The diagnoses were made only at autopsy. Neither of the patients had been examined by X-ray.

The Municipal Hospital, department I, case record no. 1124/55.

63-year-old woman; 2 years earlier gallstone attack with icterus; later several slight attacks. Present attack began 8 days ago with violent intermittent pain under right curvature. Since then, daily attacks with nausea and vomiting, increase of temperature to 40 degrees. No defecation for 4 days, no flatus. At hospitalization she was weak, confused, temperature 39.6 degrees. Pulse 104. Blood pressure 100/70. The abdomen was soft, somewhat meteoristic; slight tenderness in the gallbladder region, but no distention or defense. Treatment with penicillin and streptomycin as well as blood transfusion. However, the patient soon weakened. Eight hours after hospitalization she became unconscious and shocked, with blood pressure 80/60, pulse 120. Temperature 39.6 degrees. Abdomen unchanged. Died 16 hours after hospitalization.

Autopsy: cholecystitis acuta cum perforatione ad duodenum. Ileus e calculo vesicae felleae (1 m from the ileo-coecal region a $2 \times 2 \times 2$ cm firm, granulated stone, obturating the entire lumen).

The Municipal Hospital, department V, case record no. 1711/45.

56-year-old woman; 6 months earlier gallstone attack with a temperature of 39 degrees. The present

attack began 14 days prior to hospitalization with pain under the right curvature, accompanied by nausea and vomiting; temperature 39 degrees. After 8 days, well-being for 48 hours, then once more pain and subfebrile condition, temperature 37.8 degrees. Defaecation only after enema. On hospitalization she was congested, cyanotic. Temperature 37.5 degrees, pulse 84. Abdomen adipose, soft, without tenderness or distention. Blood pressure 110/80, haemoglobin per cent 119, blood urea 233 mg per cent, urine: — ve bile pigment, — ve urobilin. Diastasis 200. Gynaecologic examination: nothing abnormal. Rectoscopy: nothing abnormal. During hospitalization there was still nausea and a few attacks of non-feculent vomiting. No defecation, doubtful flatus. No pain. Abdomen still soft, no tenderness.

The patient weakened in spite of fluids parenterally. Died in shock 6 days after hospitalization.

Autopsy: ileus e calculo vesicae felleae (1½ m from the ileocoecal region hen's egg sized gallstone, obturating the lumen completely, the intestine proximal to this region dilated). Cholecystitis acuta perforativa. Fistula cholecystoduodenalis.

DISCUSSION

As mentioned, gallstone ileus is a relatively rare complication of gallstone disease. Naturally, the disease occurs almost solely in non-cholecystectomied patients, and in this connection it should be mentioned that during follow-up examinations of 526 conservatively treated gallstone patients, 5 to 20 years after the gallstones had been diagnosed, J. Lund found that 3 patients had had gallstone ileus.

Gallstone ileus occurs most frequently in women, and especially in elderly women. The majority of cases are found in the age group of 60—70 years. Bierring and Bohn, among other investigators, illustrated the higher complication frequency within this age group, when in 607 patients operated on for gallstone they demonstrated an increasing frequency of stones in the deep biliary passages in elderly patients; and Lyndrup, in a material of 272 conservatively treated patients, found gallbladder perforation in 5.6 per cent of the patients under 60 years, but 12.4 per cent in the group over 60 years. Shore described 7 cases of gallstone ileus; all the patients were females, the average age being 86 years. Denneen and Broderick found 10 cases, 9 of which were females, average age 64 years. As mentioned, our material comprises 17 patients, 13 of them females, average age 65.4 years.

To induce ileus, gallstone must be of a certain size, usually more than 2.5 cm in diameter. In our material the smallest stone was "walnut sized", a single stone was "the size of a hen's egg". The form and surface of the stone is of a certain importance; thus it is easier for round and smooth stones to pass than it is for irregular and rough ones. Gallstones, sufficiently large to obturate the alimentary canal, may in rare cases pass from the gallbladder via the biliary passages to the alimentary canal. Thus, in one of our patients no sign of perforation was found at autopsy. Presumably the large concrement had passed the enormously dilated ductus choledochus. Far more frequent is a perforation of the gallbladder or the choledochus, whereby the stone passes direct into a section of the intestine. Bohn called attention to the fact that solitary gallstones are more liable to induce empyema or hydrops in the gallbladder than are multiple stones, *viz.,* 35 per cent as compared to 14 per cent, and that perforations of the gallbladder were found in 6 per cent of the cases with solitary stones, as compared to 1 per cent in the group with multiple stones. In just under half the cases the cause was partly the squeezing of the stone into Harrtmann's pouch, leading to hydrops or perhaps empyema, partly the clamping-off of the arteria cystica with wall gangrene, usually in the fundus, where a possible perforation is most likely to occur.

Perforations to the duodenum are the most common phenomena; in our 17 patients we found such perforations in 5 cases, 2 of them verified by operation, 3 by autopsy. Less frequent are perforations to the ventricle, the jejunum, or the colon. In the case of a perforation to the colon, even large stones may be seen to pass, and gallstone ileus rarely occurs. In the literature from 1893 to 1953 Holm-Nielsen and Linnet-Jepsen found but 25 such cases described, Lampe reported 2 cases, and Bjørnberg 1 case.

Several stones may pass to the intestine; this may especially be suspected if the stones are found faceted, and in such cases a particularly careful palpation should be made of the entire intestine during the operation. In most cases the obturation occurs in the lower, narrowest part of the ileum (10 of our patients).

Approximately 3 per cent of all "intestinal obstructions" (ileus cases) are induced by gallstones (Sperling). In our material the figure was 4.3 per cent. The obturation is often incomplete, which corresponds clinically to the protracted course; the stone may move, and even large stones may be discharged spontaneously.

The symptoms, characterized by the underlying cholecystitis most often present, — *viz.,* perforation of the stone into the intestine, and subsequent obstruction of the intestine — are often uncharacteristic or intermittent, corresponding to the fact that the perforation from the gallbladder to the intestine may be accompanied by a spontaneous cessation of pain, after which the patient — in the course of hours or days — shows increasing signs of ileus. In 6 of our patients there were free intervals, lasting in one patients for 48 hours.

The patients have frequent attacks of vomiting, sometimes feculent; the abdominal pain may be intermittent, most frequently beginning under the right curvature. Violent pain, like that seen in

strangulation ileus, is not normal. The temperature is often increased, perhaps subfebrile, generally indicating cholecystitis. In 10 of our patients it was 38—40 degrees. Two of our patients had a slight icterus. There may be defaecation and discharge of flatus at a late stage. Retention of flatus occurred in only 6 of our patients.

The abdomen is often soft, slightly meteoristic; distinct meteorism occurs at a late stage, and especially in obstruction of the colon. There may be tenderness under the right curvature (cholecystitis!), perhaps distention or resistance as in 4 of our patients.

The patients often appear late for treatment. Nemir mentions an average duration of the symptoms of 5.4 days in a material of 8 patients; Lampe (20 patients) states 9 days; in our material the duration was from 7 hours to 14 days, with an average of 4.2 days. The general condition may therefore be greatly influenced, showing signs of dehydration as well as distinct changes in the liquid-salt balance.

As a consequence of improved diagnostic aids we can now make the diagnosis pre-operatively in many cases where it was not possible to do so before. Thorough histories and careful examinatiens are necessary. Signs of intestinal obstruction and a history of gallstones in elderly patients should arouse suspicion of gallstone ileus. Nine of our patients had previously had attacks of gallstones.

Radioscopy enables us to make certain or tentative diagnoses in most cases. A close inspection of X-ray pictures is essential. Demonstration of concrements in the intestine renders the diagnosis certain. Nørgaard describes 3 cases of gallstone ileus, diagnosed pre-operatively; in 2 of the cases roentgen-negative stones were involved, demonstrated by the presence of air in the small intestine. Air in the biliary passages should arouse suspicion of perforation to the intestine; on the other hand, Petren holds that this may be due to the presence of bacteria, "affection" round the papilla Vateri, or passage of concrements via ductus choledochus. In 5 of our patients air was found in the biliary passages.

Petren employs a contrast medium per os, and V. Drucker recommends the injection of a contrast medium through a Miller-Abbott tube, led down to the region of obstruction; some hours later the contrast medium will reveal any concrement present. Both these examinations are time-consuming, often impracticable, and they may greatly delay a possible operation.

As mentioned, we found in our material, in 13 X-rayed patients, 12 cases of mechanical ileus of the small intestine, indication in itself for operation; in 9 of the cases the most likely diagnosis was gallstone ileus. In 1 patient the X-ray examination gave no guidance. When the patient was operated on 7 hours later the ileus of the small intestine was found, and it is to be presumed that repeated examination would have indicated this.

Four patients were not X-rayed; 2 of them underwent operation on the suspicion of appendicitis acuta; in both cases a slight distention of the intestine was found proximal to the concrement. Two patients were not operated on, but died without diagnosis; in both cases, signs of ileus were found at autopsy. It is likely that an X-ray examination of these patients would have resulted in at any rate, a diagnosis of ileus.

The treatment of gallstone ileus should be operative: laparotomy and extirpation of the stone by enterotomy, although, as mentioned, spontaneous discharge of even large gallstones has been observed.

Crushing the stone has been employed (Aird). In this treatment the intestinal wall is protected by several layers of moist gauze; the stone is subjected to an increasing pressure by a forceps; if the stone can be crushed, the fragments will be "milked" down into the coecum, from where they can pass per rectum. This method is, however, not quite safe, and it cannot be recommended.

In 2 cases Kapel manipulated the stone to the colon without enterotomy, a method which Holm-Nielsen deprecates. In spite of the larger colonic lumen, the stone may again be impacted in the colon owing to spasm.

In all the cases of our material, the operational method was enterotomy with extirpation of the stone after prior oral dislocation of the stone, where this was possible, with a view to avoiding an incision in the obstructed region, where healing conditions no doubt are poorer.

The mortality of gallstone ileus was formerly very high, 50—60 per cent (Sperling and Krebs); during recent years, however, it has substantially decreased (Lampe 35 per cent); in our material 29.4 percent. Several circumstances contribute to the high mortality: the patients are elderly people; complications, particularly cardiopulmonary, are not infrequent; the diagnosis is difficult to make, and is often made at a late stage; when the patients present for treatment, pronounced disturbances in the liquid-salt balance may by present.

Out of 5 deaths among our patients, 2 died from complications in spite of operation and otherwise adequate treatment. One patient died in shock 4 days after the operation. Two cases were not diagnosed; the patients were weak and shocked on hospitalization, and died after a period of 16 hours and 6 days, respectively. In both these cases the patients had been confined to bed at home with vague uncharacteristic symptoms, and in the department neither of them showed such objective signs of ileus as to indicate an X-ray examination, which might have resulted in a diagnosis. Improved diagnosis would help to reduce

the mortality; in this connection it is worth stressing the importance of radiological examination of patients with uncharacteristic abdominal attacks, particularly elderly patients, who have suffered from gallstones earlier; further, careful pre- and postoperative treatment is necessary, including the re-establishment of normal liquid-salt balance.

However, high mortality which still prevails in connection with gallstone ileus, as well as other complications of gallstone disease, is a strong argument for an early cholecystectomy in all gallstone patients who do not present serious contra-indications; and the fact that gallstone ileus is seen mainly in patients with solitary stones, should entail careful consideration of cholecystectomy even in patients who have not had symptoms from the bile ducts, but in whom an X-ray examination, made in some other connection, has revealed solitary stones in the gall-bladder.

SUMMARY

A material is presented of 17 patients with gallstone ileus, treated in the I and V departments of the Municipal Hospital, Copenhagen, during the years 1944 to 1960. The occurrence, symptoms, diagnosis, treatment and mortality of the disease are discussed. It is stressed that the mortality is still high, 29.4 per cent in the present material; this is primarily due to diagnostic difficulties, an uncharacteristic, variegated, often subacute course, and consequently late hospitalization.

SUMMARIO

Olaf Agner, Leif Kuld Hansen e *Ole H. Iversen:* ILEO EX CALCULO BILIARI

Es presentate un material de 17 patientes con ileo ex calculo biliari. Illes ha essite tractate in le departimentos I e V del Hospital Municipal de Copenhagen durante le periodo 1944—1960. Es discutite le occurrentia, symptomas, diagnose, tractamento e mortalitate del maladia. Es sublineate, que in le material presente le mortalitate es ancora alte. Iste facto es primarimente debite a difficultates diagnostic, a un curso noncharacteristic, cariante e sovente subacute, e consequentemente a hospitalisation tarde.

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SALMONELLA TYPHI-MURIUM MENINGITIS IN A NEWBORN INFANT

By ULLA BOESEN

The first case of Salmonella meningitis was described by Gohn in 1908, the causal organism being later identified as *S. paratyphi B.*

Out of the approximately 200 cases of Salmonella meningitis published (of which 151 were collected from the literature by Henderson in 1948) only 22 were due to infection with *S. typhi-murium* and, of these, the diseases terminated fatally in 18 cases. As the source of infection was only found in isolated cases and as no patient was definitely infected directly in connection with delivery, as is presumed to have occurred in the author's case, publication is considered justified.

CASE HISTORY

A male infant aged two days was admitted to hospital on May 24, 1960, for care while the mother was hospitalized. The delivery was uncomplicated and took place at the expected time in a clinic. The birth weight was 3,000 g. A week prior to the delivery, the father and, later, two sublings had diarrhoea. The mother was admitted to hospital on account of diarrhoea and pyrexia which had been present from the day prior to delivery.

The infant, who did not present any particular symptoms, was slightly jaundiced on admission, the temperature was 37.2° C (99° F) and the umbilicus was slightly moist but not evil-smelling. Otherwise, nothing abnormal was found.

On the third day of life, the temperature had risen to 37.7° C. The infant was restless and kicking and screamed occasionally. The fontanelle was normal, no neck rigidity was present, the Brudzinski-reflex was doubtfully positive, no dermographism was present and the turgor was slightly subnormal. The infant had passed two apparently normal stools. The cerebrospinal fluid was yellow, cloudy with 12,800/3 erythrocytes, 2,500/3 leucocytes (36 per cent polymorphonuclears), protein 164 mg/100 ml, CSF sugar 40 mg/100 ml (blood sugar 70 mg/100 ml). Other laboratory investigations: Hb. 127 per cent, erythrocytes 6.1 million/mm^3, leucocytes 2,600 (7th day 18,000), differential count: polymorphs with rod-shaped nuclei 26 per cent, polymorphs with segmented nuclei 22 per cent, monocytes 12 per cent, lymphocytes 36 per cent, metamyelocytes 4 per cent.

Despite the treatment instituted, (see Table 2) the general condition of the infant deteriorated considerably. There was increasing cerebral screaming, quiver, definite neck rigidity and a positive Brudzinski's sign. On the fifth day, a generalized seizure occurred. The infant could no longer suck. The abdomen became increasingly distended and meteoritic, no intestinal sounds were heard and no faeces passed and a straight x-ray photograph of the abdomen showed ileus (dilated coils of small intestine with fluid levels).

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On the fifth day, the results of culture from the infant's CSF and the maternal faeces were available and showed Salmonella typhi-murium.

The condition of the infant deteriorated further. The infant developed tremor on being touched, grimaced and was slightly cyanotic. On the eighth day, oedema developed around the eyes and later became generalized. The diuresis remained good. The infant became pale, did not react, was cold and rigid but the tension in the abdomen diminished.

From the eleventh day, the infant was able to drink increasing quantities of milk although with occasional regurgitation which, on the thirteenth day, was slightly blood-stained and associated with slight bleeding from the upper respiratory tract. On the thirteenth day the ileus was relieved. As on the third day, the greenish stools contained *Salmonella typhi-murium.*

Despite treatment with lacto-Y and antibiotics, only transiently negative cultures were obtained from the faeces, nor did the findings in the CSF return to normal (Table 1). No bacterial growth was obtained from the specimens.

Table 1.
Cerebrospinal Fluid.

		Leucocytes	Protein
7th week	Lumbar puncture	17000/3	2600 mg/100 ml
"	Subdural puncture	3040/3	2320 mg/100 ml
"	"	4240/3	2360 mg/100 ml
9th week	Lumbar puncture	294/3	550 mg/100 ml

The general condition improved slightly. The infant gained weight but remained anaemic with a haemoglobin of about 60 per cent despite iron therapy. The circumference of the head increased: 3rd day: 33 cm, 7th week: 37 cm and 11th week 39 cm. On touching the infant quiver occurred. The infant did not react either to noise or light and contact could not be established. In the ninth week, the EEG was grossly abnormal with independent spike foci in the left and right temporal and central leads. Thus, severe cerebral damage was proved.

During the third and fourth months, the condition gradually deteriorated. On Aug. 30, 1960, the infant developed pyrexia and death occurred four days later (106th day).

Autopsy: The brain was covered with a copious layer of yellow pus. The brain was grossly oedematous, the sulci were obliterated and the cerebral tissue soft and pus-filled. Microscopic examination of the cerebral tissue showed extensive severe acute purulent meningo-encephalitis.

Table 2.
Treatment.

Preparation	Day of Life	No. of Days
Sulphacombin 1 + ½ g × 4	—	2
Penicillin 100,000 U × 2	—	2
Streptomycin 50 mg × 2	—	2
Sulphathiazole 750 mg i. v.	———	12
Chloromycetin 500 mg i. v.	———	12
" 200 mg × 3	——— ———	11 + 11
Terramycin 25 mg × 3	———	12
Phalylsulphathiazole ½ g × 2	———	10
	3 10 20 30 40 50 60 70	

Treatment: In addition to the therapy recorded in Table 2, the patient was tube-fed from the fifth to the seventeenth days and intravenous fluid therapy (glucose solution, isotonic saline, blood transfusion 30 ml × 3), oxygen therapy (tent) and intermittent gastric aspiration were administered and chlorpromazine and luminal were employed to combat tremor and seizures.

Epicrisis: An infant born to a mother suffering from pyrexial gastro-enteritis showed slight meningeal symptoms at the age of three days and proved to be suffering from purulent meningitis produced by *Salmonella typhi-murium* (which organism was demonstrated simultaneously in the mother).

The infant's umbilicus was moist and later became evil-smelling and was probably the site of the original infection. Despite very energetic treatment instituted early with sulphonamide drugs and Chloromycetin by intravenous infusion, (and later on account of persistent excretion of Salmonella in the faeces, Chloromycetin and Terramycetin were administered orally) the infant developed severe cerebral damage and died at the age of 106 days still suffering from purulent meningo-encephalitis.

DISCUSSION

In 1957, Watson (11) drew attention to the fact that the improved prognosis for meningitis after the introduction of chemotherapeutic and antibiotic agents did not apply to neonatal meningitis where the mortality remained practically as 25 years previously. Cases which develop within the first 28 days of life are considered as neonatal meningitis. Out of 45 cases, of which 73 per cent were due to coliform organisms, 29 (64 per cent) died while 11 per cent developed serious sequelae.

Smith (8) collected 409 cases of meningitis in children. The mortality for the total group was 31 per cent and for infants under the age of one month 67 per cent (24 out of 36). Eighteen per cent developed sequelae.

The same author found the ratio between Salmonella meningitis and other forms of meningitis to be 1:55.

Various theories have been propounded to attempt to explain the much greater incidence of Salmonella meningitis in children than in adults. No significant difference exists in the incidence of Salmonella gastro-enteritis. Watson (12) mentions the greater permeability of the mucosa of the gastro-intestinal tract to bacteria, the greater sensitivity of the meninges and the lesser ability of infants to form antibodies. Henderson draws attention to the observation that out of 144 cases, five were preceeded by meningococcal meningitis and two by syphilitic infection of the central nervous system.

As with other forms of meningitis, the prognosis for Salmonella meningitis improves with increasing age. Watson (12) found the results shown in Table 3.

Table 3.
Prognosis According to Watson.

Age	Number of Cases	Percentage Mortality
Less than 30 days	67	94
30—90 days	20	85
90 days—1 year	26	89
1—15 years	18	67
Over 15 years	12	75

Watson included all published cases in his series so that many of the patients only received symptomatic treatment and only a few were subjected to treatment with broad-spectrum antibiotics.

In the same article, a comparison was undertaken between the prognoses for meningitis caused

Table 4.

No.	Ref.	Year	Age	Treatment	Course
1	(10)	1945	6 months	Sulphapr.	Satisfactory
2	(9)	1945	13 months	Sulphapr. + Pen.	Healthy
3	(2)	1948	5 months	Sulphapr. + Pen. + Streptom.	Died after 36 hours' therapy
4	(1)	1949	17 days	Streptomycin	Died on 8th day
5	(5)	1950	11 weeks	Sulphapr. + Pen. + Streptom.	Healthy
6	(5)	1950	4 months	Sulphapr. + Pen. + Streptom.	Recurrence on 33rd day Death 35th day
7	(6)	1950	11 days	Sulphapr. + Streptomycin	Healthy
8	(7)	1954	3 days	none	Death on 6th day Diagnosis at autopsy
9	(4)	1958	5 months	Pen. + Streptomycin	Death on 11th day

by various forms of Salmonella bacteria. The mortality was found to be lowest for *S. paratyphi B:* 59 per cent and highest for *S. enteritidis, S. havana and S. paratyphi-murium* where it was 100 per cent in all.

Thirteen out of the 22 published cases of *S. typhi-murium* meningitis, were collected by Henderson (3) in 1948. The ages of the patients varied between six weeks and eight months and the mortality was 100 per cent. One of the patients had suffered from meningococcal meningitis two weeks previously. No information is available concerning the source of infection nor the chemotherapy or antibiotic treatment instituted.

The data concerning the remaining nine cases is summarized in Table 4.

In three of the abovementioned cases, the source of infection is considered to have been established:

In Case No. 3, *S. typhi-murium* was found in the maternal faeces. The mother was healthy but one of the infant's older siblings had suffered from diarrhoea a week prior to the patient's illness. No bacteria could be found in the siblings.

In Case No. 7, a nurse who attended the patient was found to excrete *S. typhi-murium.*

Case No. 9 was placed for the first 12 hours of life in a ward with a child who had later to be isolated on account of gastro-enteritis. Both in this child and its mother *S. typhi-murium* were found on culture from the faeces. The mother of the patient was not examined.

In the present case, the mother had *S. typhimurium* gastroenteritis which was producing symptoms at the time of delivery. It must be presumed that the infant was infected during delivery, probably via the umbilicus which was moist on admission and later evil-smelling. Lactation had not yet commenced so that channel of infection, which has been mentioned as a possibility in connection with the previous cases of Salmonella infection may be excluded.

Only four patients recovered from *S. typhimurium* meningitis and these will be briefly mentioned:

Case No. 1 was a boy aged six months who was admitted with pyrexia, vomiting, unilateral seizures, ocular deviation, positive Trousseau's sign, tense fontanelle, slight neck rigidity and rhinopharyngitis but no symptoms of gastro-enteritis and two negative cultures from the faeces. The treatment consisted of sulphapyridine and sulphadiazine orally and intramuscularly for 12 days.

Case No. 2 was a girl aged 13 months who was admitted following respiratory infection and small vomits for two weeks. No signs of meningitis were present. The child was treated with penicillin for pneumonia. Lumbar puncture was undertaken on account of seizures and revealed purulent meningitis and, therefore, therapy with sulphadiazine, oxygen and sedatives was instituted in addition. The temperature was normal by the 13th day. Antibiotic therapy was withdrawn on the 27th and 19th days.

Case No. 5 was a girl aged 11 weeks who had been irritable and subfebrile with respiratory infection for two weeks. One week previously, one of her siblings had had loose green stools. On admission, the temperature was high, the fontanelle was firm but not tense, Brudzinski's reflex was positive but there were no other signs of meningitis. Pharyngitis was present. Following lumbar puncture, treatment with penicillin, sulphadiazine and streptomycin was instituted. The patient improved and by the 17th day the CSF was normal and the patient showed merely anaemia. Following treatment with streptomycin orally for four days, the faeces no longer contained *S. typhi-murium* but ten days after withdrawal of the drug, bacteria were again found but disappeared finally after further oral streptomycin treatment for ten days.

Case No. 7 was a boy aged 11 days who was admitted after violent diarrhoea for 24 hours. On

the fourth day, there were signs of meningitis. Treatment with sulphadiazine and streptomycin for 30 days was instituted with good effect. Two weeks later, recurrence took place and was treated with streptomycin intramuscularly and intrathecally. Gradual improvement occurred and the infant was discharged on the 110th day.

It will be observed that cure was effected by treatment with a sulphonamide preparation alone and in combination with penicillin and streptomycin while the same preparations were without effect in other cases. In the present case, treatment with Chloromycetin was also instituted with transient improvement but the patient not only developed cerebral damage but continued to excrete bacteria and recurrence took place later. This poor result occurred despite the fact that treatment was instituted at such an early stage of the disease that the symptoms would not have been observed at home.

SUMMARY

A case of *Salmonella typhi-murium* meningitis in a boy aged three days is reported. The infant was presumably infected from the mother via the umbilicus during delivery. Treatment with sulphonamide preparations and broad-spectrum antibiotics was commenced on the appearance of the first symptoms but, nevertheless, the condition deteriorated considerably during subsequent days. The infant gradually improved during this treatment and the administration of intravenous fluids but developed serious sequelae: cerebral damage and continued excretion of *S. typhimurium* in the faeces. Death occurred three and a half months later.

In connection with this case, a brief review is given of the 22 cases of the same condition previously published with particular attention to the source of infection and the prognosis.

SUMMARIO

Ulla Boesen: MENINGITIS DE SALMONELLA TYPHI-MURIUM IN UN NEONATO

Es reportate un caso de meningitis de salmonella typhi-murium in un puero de tres dies. Presumibilemente le infante ha incontrate le infection durante le delivrantia ab le matre via le umbilico. Al apparition del prime symptomas esseva instituite tractamento con sulfonamidos e antibioticos de large spectro. Totevia le condition se aggravava considerabilemente durante le proxime dies. Le infante meliorava gradualmente sub iste tractamento e sub le administration intravenose de fluidos, ma il se disveloppava grave sequelas: injurias cerebral e excretion continue de salmonella typhi-murium in le feces. Le morte occurreva tres menses e medie depost.

In connexion con iste caso on presenta un breve revista super le 22 casos del mesme condition previemente publicate con attention special al fonte del infection e al prognosis.

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ANÆSTHESIOLOGY CENTRE COPENHAGEN

By E. WAINØ ANDERSEN, W. DAM, E. HUSFELDT, B. IBSEN, J. KIRCHHOFF, H. RUBEN and O. SECHER

At the first congress of the Scandinavian Society of Anaesthesiologists in Oslo (1950), the representative of the World Health Organization—Dr. Erwin Kohn—clearly presented the arguments which made the WHO decide to sponsor and support postgraduate training of anæsthesiologists. The major argument was the importance of this specialty in terms of "public health" or —in other words—the understanding of a relationship between improvements in anæsthesia services and decrease in morbidity and mortality in a population of hospital patients. That this relationship is *now* widely accepted as existing is clearly demonstrated by the growing interest in training anæsthetists and establishing anæsthesia departments. Furthermore it has again and again been stressed by representatives of the WHO that progress in surgery is no longer possible without continuous improvement in the triade represented by nursing care, blood transfusion services, and anæsthesiology.

The work of the Anæsthesiology Centre Copenhagen has previously been described partly as annual reports from the Centre—reports which have been sent to all Universities—partly as an address before the World Congress of Anæsthesiologists in Scheveningen 1955 and partly in an article in the Chronicle of the World Health Organization (1958). Referring to these earlier publications the present work will give only a brief description of the Centre as it was and as it is; the main emphasis will be put on a discussion of the problems around postgraduate training in anæsthesiology which the one year courses have raised and a presentation of the ideas behind the attempts to solve some of those problems.

The Centre was inaugurated in Copenhagen on May 3, 1950, and its establishment was due to the fact that Denmark was lagging behind as far as anæsthesiology was concerned—there was no recognized specialty in the country, there were only a few hospital posts for anæsthetists and there was a mere handful of physicians who had declared themselves for the specialty. In this situation WHO had offered the Faculty of Medicine at the University of Copenhagen—through the Danish National Health Service—to give assistance, mainly in terms of medical consultants. As these medical consultants were teaching in the English language, provision was also made for participation of trainees from countries other than Denmark. Over the first three years trainees came only from Europe and mainly from the Scandinavian countries; then fellows were successively brought to Copenhagen also from the Eastern Mediterranean Region, the African Region, the South East Asian Region, the Western Pacific Region and a few years ago the American Region so that by now all six regions under WHO have been represented by fellows.

In the first 11 courses a total of 160 fellows from the following 45 countries have participated: Austria, the Bahamas, Belgium, Brazil, Bulgaria, China, Costa Rica, Czechoslovakia, Egypt, Finland, Formosa, France, Germany, Greece, Hong Kong, Iceland, India, Indonesia, Iraq, Iran, Ireland, Italy, Japan, Jordan, Korea, Lebanon, Norway, Pakistan, Peru, Philippines, Poland, Portugal, Portuguese India, Portuguese West Africa, Portuguese East Africa, Saudi Arabia, Spain, Sweden, Switzerland, Syria, Thailand, Turkey, U.S.S.R., and Yugoslavia.

Danish physicians and others—totalling 171—have participated during employment at the anæsthesia departments of hospitals affiliated with the Centre and many trainees have followed the courses for more than one year.

In 1950 the six hospitals (Amtssygehuset i Gentofte, Bispebjerg Hospital, Finseninstitutet, Kommunehospitalet, Orthopædisk Hospital, and Rigshospitalet) could offer approx. 25,000 anæsthetics a year as the basis for practical instruction—in 1960 approx. 60,000. After 1954 each of the hospitals has had its own separate anæsthesia department. In the first course 40 per cent of the teachers came from abroad, in the 5th course 25 per cent and in the 10th course only five per cent. Intentionally, the development has thus been that more and more of the teaching—which was originally covered by the WHO Medical Consultants—has been taken over by the Danish instructors and lecturers.

At present, a one year course consists of training in anæsthetic technique and teaching in the theoretical basis for anæsthesiology. In the technical training uniformity is deliberately avoided so that techniques may vary a great deal from hospital to hospital. The teaching is offered as lectures, colloquia, trainee lectures with discussion, morbidity and mortality meetings, demonstrations, special courses (bronchoscopy) and

Read before the 6th Congress of the Scandinavian Society of Anæsthesiologists, Gothenburg, Sweden, June 30, 1960.

films. Within the 9th course Professor Zaimis from London gave a "course in the Course" at which the mode of action of curarizing drugs was demonstrated in experiments on a number of different species.

The teaching programme is supplemented by running daily conferences at the hospitals. One of the hospitals — Bispebjerg — has offered all through the years a daily evening conference where interesting cases are presented along with a more didactic presentation of planned topics. This particular conference has always been followed with great interest by the visiting trainees.

On the whole the efforts of the staff are directed towards creating an atmosphere among trainees and instructors in which they think along the same lines and "speak the same language" or in other words direct their attention to the problems — big or small — which the daily administration of anæsthetics will necessarily raise.

In discussing postgraduate teaching it is important at all times to keep in mind what one is aiming at or — expressed differently: What "finished product" is it that we would like to hand back to his country once he has passed the course and the final examinations?

Even though the Copenhagen Centre by no means can or will try to produce fully trained specialists in anæsthesiology it may be useful in this connection to recall the criteria set up by Mushin in 1956 as characteristic for the specialist in anæsthesia. Generally he suggested that he should be a physician with "a wide and sound knowledge of the medical field as a whole, with breadth of vision essential to a balanced and critical outlook". Further Mushin envisaged a suitable basic training in the humanities as well as the basic sciences. And: "In addition he must be a mature personality aware of the life of the community around him and able to sense almost subconsciously the needs of the community and of medicine in terms of his own specialty, and so to develop an acute if subconscious sense of time and place for advance and development". Among the more specific qualifications Mushin mentions first and foremost technical proficiency. Then a wide knowledge and understanding of the physiological and pharmacological processes involved in the administration of anæsthetics. Temperamentally and educationally the specialist must be fitted for this particular type of work and he must be a mature type of doctor with a sympathetic approach to patients in pain and/or fear. Further he should be able to transfer his special knowledge to problems in other fields. Mushin's last aim is ".... to produce an individual well able to advise administrative authorities on problems connected with his work, and to take part in the complex machinery of modern hospital life".

Mushin deliberately omits the ability to teach and to conduct research. It is desirable that the specialist has these abilities but they are not considered fundamental requirements of the specialist "whose real and primary function is to serve the daily needs of the community for anæsthesia as an adjunct of surgical treatment".

If the above concept is accepted it is reasonable to ask what the aims of the Copenhagen training centre are. Is it to give basic teaching to physicians with no previous knowledge of anæsthesia? Is it to give further training to physicians who already have some experience in anæsthesia or is it to offer higher education in the latest advances within anæsthesiology? Nobody will be surprised when we state that there is no clear answer to these questions. It will have to be recalled that the courses were instituted because Denmark was an underdeveloped country as far as anæsthesia was concerned. Further it has to be considered that the selection of trainees to a large extent is based on financial deliberations since by far the largest contingent of trainees come from countries eligible for Technical Assistance in accordance with the criteria set up by the United Nations. Therefore the situation is usually that 10 per cent of the fellows are specialists in anæsthesia in their home country, 10 per cent are fellows with no previous training in the specialty while the remaining 80 per cent have more os less previous experience. Keeping in mind the variation in status of the specialty from country to country no strict criteria are set up for admission to the course. This is so because one does not want to run the risk of excluding a trainee coming from a country where the specialty has not yet been established. That trainee will have the possibility of returning from a course and be instrumental in having the specialty recognized as an important part of the pattern in the health system of his particular country. In assessing a teaching activity such as the Anæsthesiology Centre it does not seem to make sense to attempt to teach such a heterogenous group of trainees. All we can say to this is that in actual practice it is possible to reach results which would seem impossible. Part of the explanation is that six hospitals are working together so that it is possible to offer training in all types of anæsthesia ranging from a minute local anæsthetic to anæsthesia for surgery on the open heart with or without hypothermia. Because of this the physician with no prerequisites as far as anæsthesia is concerned receives the most basic teaching and may then be able to find out whether he has chosen the right specialty which will suit his temperament. If this is the case he may receive advice and possibly other kinds of assistance from WHO in his future work. Trainees with some previous experience get the opportunity to study new and different techniques which may enable them to get a more balanced opinion in selection

of treatment for the individual patient. Finally, the one who is already a specialist gets the opportunity to dig into more special problems according to his interest and inclination.

As regards the theoretical teaching this is no place for a detailed account, considering that a particular curriculum will always depend on a number of local factors the most important being availability of suitable teachers. A comparison between the first and the tenth courses shows that the number of teaching hours has expanded by 30—40 per cent. It further appears that the "activating" methods of teaching have replaced formal lectures to a considerable extent. In the early period around 95 per cent of the teaching was delivered as lectures. After ten years only around 50 per cent of the teaching is in lecture form. The sequence which — at least at present — seems to lead to the best results is the one, where a certain subject is covered by one or two systematic lectures, which are then followed by a series of discussion groups or colloquia with an instructor as moderator and with active participation of the trainees. Especially as far as the basic sciences are concerned this has turned out to be a practical approach. In the initial phase of the function of the Centre it was a little difficult to find a quite satisfactory method of covering applied physiology, pharmacology, anatomy and pathology. The sequence described seems to be a useful compromise between on the one hand the lecture by a basic science teacher and on the other the basic science lecture given by a clinician.

The question of desirability of a final examination has been under perpetual debate from the very first day. Among the Danish teachers there was a good deal of opposition in the beginning — mainly because it was against Danish medical tradition to have postgraduate examinations at all. This point of view has changed completely over the years. At present it is the consensus of opinion among the staff that it is impossible to run a satisfactory course unless interim examinations are held regularly and unless a final examination is held at the end of each course. Therefore the final examination is now set by the Faculty of Medicine of the University of Copenhagen and successful candidates receive a diploma signed by the Dean of the Faculty. Selection of the type of examination has not created very much excitement. We are aware of the fact that the "essay type" has fanatic supporters in certain quarters while the "multiple choice type" is just as fanatically supported from other quarters. As a result we have been using both methods as well as modifications and in general we find that the results obtained by the individual trainee are pretty consistent irrespective of the type of examination he is exposed to.

For many years, WHO as well as the staff was interested in evaluating the results of these courses. It was thought that one might obtain *some* information by studying the fate of previous trainees in their home countries. Questionnaires were sent out and we found that a certain number were leading departments of anæsthesia, a certain number were full time anæsthetists, others were working full or part time in other specialties, etc. We also found, however, that it is quite impossible to establish any relationship between the fact that a particular physician has taken a course in Copenhagen and the fact that he has been able to place himself at a certain level in medicine, teaching or research in his home country. But still the question of evaluation was considered urgent all the time — not least since it became more and more desirable to confirm that the allocations recommended by WHO and the Danish National Committee for Technical Co-operation were used in a sensible manner. This was the reason why Professor Woolmer from London was invited to evaluate the course as such in the summer of 1960. He could do so on the basis of earlier observations during his period as Medical Consultant in the second course, of reports written by former trainees and consultants, of a study of the curriculum and of the background, criticisms and wishes of trainees in Copenhagen at that time (10th course). In a very positive manner Professor Woolmer pointed out the weak points of the teaching at the Centre and part of his conclusions was that Copenhagen was the right place for courses such at these and that the courses were being conducted along the right lines.

As far as Denmark is concerned it has already been mentioned that before the inauguration of the Centre there was only a handful of physicians interested in the specialty and there were no positions as heads of department matching similar positions within other specialties in medicine. According to the latest figures (in 1959) Denmark now has 49 heads of department of anæsthesia. Out of these 39 have taken the course one or several times. Among the remaining ten, seven have had similar training in the UK or the U.S.A. From these figures it seems reasonable to conclude that Danish anæsthesiologists as a body consider it important if not absolutely necessary to take the course. But then again we have to correct for the fact that participation in a course offered certain technical advantages over the first few years as far as specialist recognition and increments in salary were concerned.

In 1955/56 the opinion began to grow that courses of the type described above should be limited to a certain — and not too long — period of time and that it would be necessary to offer supplementary courses of shorter duration. Refresher courses were then planned. It turned out, however, that the interest in sending trainees for the one year courses continued to

grow. This has not stopped continued planning work concerning refresher courses and at the moment invitations are being sent to former trainees from the first five courses living in countries eligible for Technical Assistance. The first refresher course will begin on October 2, 1961 and last for ten working days. Twenty-four trainees have been invited and further WHO has invited one Medical Consultant from abroad and two or three lecturers. The main purpose of the course will be to study — via direct contact — the impact of the teaching in the Anæsthesiology Centre on anæsthesiology in the countries from which these 24 trainees are coming. At the same time the trainees will have the opportunity to study possible progress in the Copenhagen hospitals and they will be offered a teaching programme involving recent advances in the specialty.

The Anæsthesiology Centre Copenhagen started in 1950 and most colleagues in Denmark and other countries expected the experiment to survive for a few years only. It has turned out, however, that there was a real need in many countries for a training centre such as this.

Many mistakes have been made while the child was growing and the staff is continuously studying these mistakes — or, as we like to call it, looking back to find the future. Should the Centre ever reach perfection the staff rests assured that at that time there probably would be no need for a teaching centre.

SUMMARIO

E. Wainø Andersen, W. Dam, E. Husfeldt, B. Ibsen, J. Kirchhoff, H. Ruben & O. Secher: CENTRO DE ANESTHESIOLOGIA COPENHAGEN.

Le articulo se refere al rolo del anesthesiologia intra le hygiene public ("public health") e face mention del Centro de anesthesiologia Copenhagen. Isto esseva establite in maio 1950 per medio de un collaboration inter le World Health Organization, le Universitate de Copenhagen, e le Officio de sanitate. Ab 1957 le cursos annue ha functionate como parte del programma amplificate pro adjuta technic. Ab 1960 participantes habente passate le examination terminal post un curso annue es diplomate per le facultate de medicina del Universitate de Copenhagen.

Le prime 11 cursos comprendeva 331 participantes ex 46 paises in toto — incluse Danmark. Sex hospitales in Copenhagen alberga le cursistas, e actualmente on executa circa 60000 anesthesias pro anno in le hospitales connectite con le curso.

Le articulo cita le criterios de Mushin pro labor specialista de anesthesiologia, e super le base de su concepto on discute le activitates del curso. Un scrutinio del disveloppamento del forma del instruction demonstra, que le forma activante progrede de plus in plus.

Es describite le difficultates re le evalutation del resultatos del Centro, e on annuncia un curso de refrescamento pro ex-participantes, le qual habera loco in le autumno de 1961. Illo habera un duration de duo septimanas e tene le proposito de functionar como parte del complexo integre del evalutation.

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